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Exhaled and nasal nitric oxide measurement in the evaluation of chronic cough

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ABSTRACT

Chronic cough is one of the most common and troublesome nonspecific respiratory symptom for which patients seek a general practitioner and specialist advice. It is conventionally defined as a cough lasting for more than 8 weeks.

Exhaled nitric oxide has proven to be a specific biomarker capable to discriminate between differential diagnoses of chronic cough and simultaneously provide information about the response to specific treatment. In this review, we will discuss the potential use of exhaled and nasal nitric oxide in the diagnosis of chronic chough.

1. Introduction

Chronic cough, conventionally defined as cough lasting for 8 weeks or longer [1], is one of the most common and troublesome nonspecific respiratory symptom for which patients seek a general practitioner as well as specialist advice [1,2]. Chronic cough affects 10–20% of adult population, with a predominance in middle-aged women, obese and smokers [3,4].

Subjects with chronic cough are subdivided in affected by cough variant asthma (CVA), non-asthmatic eosinophilic bronchitis (NAEB), upper airway cough syndrome (UACS), cough related to gastro-esophageal reflux disease (GERD) and atopic cough (AC) [5–7]. In some hypertensive patients, ACE inhibitor drugs can be the causative factor of a chronic cough [8]. Other etiologies, although rare, include infections such as tuberculosis and pertussis, primary ciliary dyskinesia (PCD), tracheobronchomalacia and tracheoesophageal fistula [9].

Most of the conditions underlying chronic cough are treatable and, thus, an early and accurate diagnosis is required for specific treatment. Unfortunately, today there is no consensus on which investigations are useful in the diagnostic evaluation of chronic coughs [10]. The diagnosis is obtained through an exclusion process, which may entail multiple tests to rule out its most common etiologies [11]. Initial patient assessment includes history, symptoms pattern, pulmonary function tests and chest radiography. Subsequently, the results of this initial assessment should eventually suggest further diagnostic tests or start empirical treatment [11]. The final therapeutic success of the treatment will establish the definitive diagnosis of the chronic cough [12].

Specific tests or biomarkers capable to discriminate between differential diagnoses of chronic cough and provide information about the response to specific treatment are urgently needed. In this context, fractional exhaled nitric oxide (FeNO) has proven to be a valuable candidate.

2. Fractional exhaled nitric oxide

Nitric oxide (NO) is a free radical gas produced from L-arginine by three enzymes called nitric oxide synthases (NOS): inducible (iNOS), endothelial (eNOS), and neuronal (nNOS) [13]. eNOS and nNOS are constantly active in endothelial cells and neurons, respectively, and are involved in a variety of biological functions, including antimicrobial activity, blood flow regulation, platelet function, neurotransmission, immunity [13]. The iNOS action can be induced in states like inflammation (for example, by cytokines).

F_{ENO} levels increase during T_h2 allergic inflammation and often correlate with eosinophilic airway inflammation [14]. In fact, in

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allergic airway inflammation, mast cells and antigen-specific T_h2 cells are activated, resulting in the production of cytokines, including IL-4, IL-5 and IL-13. IL-4 and IL-13, but not IL-5, determine an iNOS upregulation, increasing the production of FENO in airway epithelial cells [15]. Recent studies suggest that FENO is a more accurate and broader marker of T_h2-mediated allergic inflammation, which includes airway eosinophilia rather than eosinophilic inflammation only [15]. Although increases in airway eosinophil counts and increases in FENO levels often occur simultaneously, several studies suggest that the cytokines that regulate the iNOS induction are separated from those regulating eosinophil traffic through the airways. This process may result in a dissociation between FeNO levels and eosinophilic inflammation [15].

NO can be measured in the exhaled air (FeNO) or in the nasal cavities (nNO). Specific guidelines have been developed for standardized FeNO measurements but not for nNO measurements, considering the chemiluminescence analysis the gold standard technique for its measurement [16]. Nowadays, other NO analyzers, mainly based on electrochemical sensor technology, have been developed [17].

Because of the correlation with airways eosinophilic cells in asthma, FeNO could be a potential indirect predictor of T_h2 airways inflammation [18,19], which appears to be highly prevalent in subjects with chronic cough, allowing for FeNO a role as a diagnostic tool in the challenging evaluation of chronic coughs [20,21].

3. Exhaled NO in bronchial asthma and cough-variant asthma

Among the conditions underlying chronic cough, the most frequent are CVA and asthma [22]. CVA is defined by current guidelines as the combination of chronic cough, airway hyperresponsiveness (AHR) and good response to anti-asthmatic therapy [11]. FeNO can play a role in differentiating chronic cough due to asthma and CVA from other causes [21], as well as to monitor disease treatment.

It was reported that in bronchial asthma FeNO correlates with AHR and with the eosinophil ratio in induced sputum, bronchoalveolar lavage and blood eosinophils [23–25]. These results were extended to patients with CVA, correlating FeNO increase with other markers of eosinophilic inflammation [21,26]. In asthmatic patients, FeNO values are significantly increased as compared to non-asthmatics with chronic cough and healthy subjects [27]. For chronic cough, FeNO values below 30 ppb indicate that asthma is not the causative factor with high probability [27]. Indeed, using a cutoff value of 30 ppb the negative predictive value for asthma has been reported to be 93%. However, values of FeNO above 30 ppb have reasonable sensitivity (75%) and weak positive predictive value (60%) for asthma diagnosis as the cause of chronic cough. Therefore, FeNO may have greater value as a negative predictive index in distinguishing asthma or CVA from non-asthmatic coughs, thus avoiding the need of more invasive tests such as bronchial challenge.

However, higher/lower values were also reported. Sato et al. [21] found in 71 consecutive patients with chronic cough an optimal cutoff value of 38.8 ppb to distinguish bronchial asthma and CVA from non-asthmatic eosinophil bronchitis and others causes of cough, reporting a sensitivity of 79% and a specificity of 91%. Kowal et al. [28] stated that using 40 ppb as a cutoff value of FeNO it is possible to discriminate chronic cough with and without asthma with a specificity and a sensitivity of 82% and 88%, respectively. Reporting lower cutoff FeNO levels, Shimoda et al. [29] differentiated asthma and CVA from healthy subjects. Namely, 20 ppb was found for healthy control *vs.* asthma (sensitivity 72%, and specificity 84%), and 28 ppb for asthma *vs.* cough variant asthma (sensitivity 69% and specificity 73%).

Based on the above studies, we conclude that the optimal cutoff levels are mostly between 30 and 40 ppb, and that FeNO has a moderate diagnostic accuracy in predicting asthma or CVA as causative factors of chronic cough. However, FeNO measurement is useful because, since it reflects the presence of airway eosinophilic inflammation, it may anticipate the response to inhaled corticosteroids [30,31].

4. Exhaled NO in non-asthmatic eosinophilic bronchitis

Non-asthmatic eosinophilic bronchitis (NAEB) is defined as a chronic cough that, similarly to asthma, is characterized by eosinophilic airway inflammation but with no symptoms or objective evidence of variable airflow obstruction and normal airway responsiveness [7]. An accepted upper cutoff level greater than 3% for non-squamous sputum eosinophils is accepted as an indication of eosinophilic bronchitis [32]. Up to 13% of patients with NAEB in specialty cough clinics presents eosinophilic airway inflammation [7,33,34], and a significant correlation between FeNO and the eosinophil percentage in induced sputum from NAEB subjects was reported [35,36].

NAEB usually well responds to corticosteroid treatment but can also be persistent, requiring long-term treatment, and, in some rare cases, it can progress toward asthma [35]. Thus, the differential diagnosis of NAEB from other causes of chronic cough is essential for therapeutic and prognostic reasons. According to the current recommendations, if NAEB is suspected to be the primary cause of chronic cough, eosinophil count on induced sputum is considered the optimal tool to confirm or exclude the diagnosis [36].

Very few studies described the potential use of exhaled NO analysis in NAEB [33,37,38], and only in one the extended NO analysis with the two-compartment model was applied [39]. All the above studies reported a significant increase of FeNO values in NAEB patients as compared to patients with chronic cough related to other causes (GERD and UACS), but no significant difference in FeNO levels between NAEB and CVA patients was observed. In two studies, a cutoff of 33 ppb was suggested as an optimal value for detection of NAEB and CVA patients, with high sensitivity and specificity [38,39].

In nonasthmatic patients with chronic cough, Oh et al. [33] indicated that a FeNO value < 31.7 ppb had a high negative predictive value (95%), reasonable specificity (76%), and a helpful negative likelihood ratio (0.19) to rule out NAEB as the primary cause, thus, avoiding the need for more invasive and time consuming tests like induced sputum examination. Yi and coworkers [37] found an optimal cutoff level for FeNO of 22.5 ppb to distinguish eosinophilic bronchitis from other nonasthmatic causes of chronic cough, but it generated relatively low sensitivity (69.8%) and specificity (76.2%). However, a recent meta-analysis using pooled data from the few studies available showed that the diagnostic accuracy to predict NAEB was low and the specificity inconsistent [40].

5. Nasal NO analysis in upper airways cough syndrome

UACS is a condition associated with a number of diseases involving the upper respiratory tract. The diseases involving the nose and paranasal sinuses most frequently cause chronic cough [5]. It is estimated that rhino-sinusitis (RS) contributes to coughing in up to 20–40% of patients presenting chronic cough and normal chest X-ray [5,41]. UACS often coexists with other diseases that can cause chronic cough such as CVA and GERD.

5.1. Chronic rhino-sinusitis

Several reports indicate that nNO is decreased in subjects with chronic RS. In a study by Lindberg et al. [42], nNO levels were significantly lower in RS patients suffering from chronic sinusitis as compared to healthy subjects (96.4 ± 72.8 *vs.* 233.2 ± 66.8 ppb, respectively), suggesting the usefulness of nNO evaluation in the diagnostic process of sinusitis-induced chronic cough. Kim and coworkers [43], by analyzing 58 subjects with UACS reported that those with sinusitis showed significantly lower nNO levels, as compared with those without sinusitis (190 ± 114.8 *vs.* 345.7 ± 114.6 ppb, respectively). Furthermore, nNO levels in UACS with sinusitis were reported to be much lower than those in non-UACS. Thus, nNO measurement seems to have the potential to discriminate sinusitis from non-sinusitis causes of

chronic cough.

In the context of chronic RS, some related factors such as nasal polyps (NP) or allergic rhinitis can interfere with the level of measured nNO, and must be taken into consideration. In a study by Jeong et al. [44], the levels of nNO were significantly lower in subjects with chronic RS complicated by polyps with respect to controls (88.5 ± 54.7 *vs.* 241 ± 89.5 ppb, respectively) [44–46]. The difference in nNO concentration observed could be linked to sinusal ostia patency: when the ostium is partially closed, the NO flow from the sinus decreases and, consequently, nNO concentration decreases.

Chronic RS can be classified according to the presence of nasal polyps, and their presence gives rise to high infiltration of tissue eosinophilia with a burst of T_h2 inflammatory cytokines. Chronic RS with nasal polyps can be divided according to the presence of tissue eosinophilia, and classified as eosinophilic and non-eosinophilic [47]. nNO measurement might be useful for classification and definition of chronic RS phenotypes. Indeed, untreated non-eosinophilic chronic RS patients show nNO levels significantly lower than normal subjects, whereas no significant difference was observed with respect to eosinophilic chronic RS patients [48].

5.2. Primary ciliary dyskinesia and cystic fibrosis

Primary ciliary dyskinesia (PCD) and cystic fibrosis (CF) markedly affect NO production. PCD is a disease associated with an anomalous structure and/or function of cilia characterized by frequent lower airways infections, chronic RS and male infertility [49]. PCD patients present extremely low concentration of nNO so that levels lower than 100 ppb are highly indicative for PCD or CF [49].

Adopting an nNO value of 105 ppb as cutoff, a correct diagnosis of PCD can be achieved with a specificity, sensitivity and positive predictive values of 88%, 100% and 89%, respectively [50], but a cutoff level of 77 nl/min was also recommended [51]. Values of nNO larger than 250 ppb are reported to exclude PCD diagnosis with 97% certainty [52], while low values of both FeNO and nNO distinguished PCD patients from other bronchiectatic patients with a specificity of 98% and positive predictive value of 92%, making the simultaneous measurement of exhaled NO and nNO a useful screening tool for PCD [53].

The extremely low levels of nNO during humming maneuver observed in subjects with PCD support the notion that NO is defective in the paranasal sinuses. A reduced synthesis of nNO may be due to reduced production or abnormal activity of nitric oxide synthase (NOS) isoforms, or to the obstruction or agenesis of paranasal sinuses present in PCD [49].

6. Exhaled NO analysis in gastroesophageal reflux disease

Cough is often related to GERD. Recent data indicated that up to 25% of chronic cough cases are associated with GERD [54], but this does not necessarily imply that GERD is the etiological cause in many of the affects individuals.

The pathogenesis of GERD associated cough is complex and the diagnostic tests available are of limited reliability. Two theories have been put forward: microaspiration of refluxate in the larynx directly enters the bronchial tree causing cough as a protective mechanism (the reflux theory); and the common embryologic origin of the respiratory and the digestive tracts (reflex theory) [55]. In a cross-sectional study involving patients with cough and GERD, and asthmatic patients with and without GERD, Parameswaran et al. [56] reported that there was no evidence of worsening of airway inflammation as measured by both sputum cell counts and FeNO. Similarly, an increase in inflammatory cell number in both bronchoalveolar lavage fluid and bronchial mucosal biopsies was observed in six patients with cough and objectively confirmed GERD [57]. The above studies seem to indicate that gastroesophageal reflux has no influence on airways inflammation and thus FeNO concentrations has no direct role in the diagnostic evaluation in patients with cough related to GER. In other words, high FeNO levels might exclude GERD.

7. Exhaled NO in atopic cough

Atopic cough (AC) is a new clinical entity described in Japan, in which patients present a chronic non-productive cough resistant to bronchodilators [58]. The fundamental features of AC include eosinophilic inflammation of the central airways, increased cough reflex sensitivity and normal bronchial responsiveness. These characteristics distinguish AC from CVA or NAEB, in which eosinophilic inflammation involve both central and peripheral airways. Fujimura et al. [26] reported that FeNO levels were significantly lower in patients with AC when compared with patients with CVA ($p = 0.0007$) or BA ($p = 0.002$), while no significant difference between CVA and BA patients was observed ($p = 0.76$). The lower levels of exhaled NO in AC may be useful in differentiating it from CVA, EB and other causes of chronic nonproductive cough [58].

8. Exhaled NO as predictor of corticosteroids responsiveness in chronic cough

Similar to asthma, a strong correlation between FeNO levels and other markers of eosinophilic inflammation in CVA and NAEB patients has been reported [37,39]. This suggests a potential role of FeNO in predicting ICS response in patients with chronic cough related to eosinophilic airways inflammation, and may be useful even in those subjects who have nonspecific respiratory symptoms (*i.e.*, chronic cough), suggesting to start a trial with inhaled corticosteroids.

The role of FeNO as a predictor of successful ICS treatment in patients with chronic cough and its advantage over other conventional measures such as spirometry, bronchodilator responsiveness and peak flow rates has been showed in several studies [59,60].

In Hahn and colleagues' retrospective study [61], FeNO accurately predicted the response to ICS in patients with chronic cough; subjects with elevated FeNO levels more likely had a positive response to treatment, while subjects with FeNO in the normal range were unlikely to respond. A FeNO cutoff point of 38 ppb was associated with the best sensitivity, specificity and with a high PPV. A similar FeNO cutoff [20] showed a high sensitivity (94.7%) in the prediction of the response to ICS. Yi et al. [37] found that a FeNO level of 31.5 ppb in patients with chronic cough could indicate the likelihood of response to empirical ICS trial, with reasonably high specificity, and PPV. Smith et al. [59] demonstrated that subjects with chronic undiagnosed respiratory symptoms who had high FeNO as baseline (cutoff point was 47 ppb) showed the best improvement in FEV_1 after inhaled fluticasone, with a NPV of 89%. By contrast, in a prospective work by Prieto et al., no correlation between FeNO and response to ICS in terms of improvement of symptom score was reported, being the variations in the group with high FeNO values similar to those with lower FeNO [62]. Nevertheless, the American Thoracic Society recommended the use of a cutoff > 50 ppb as a strong indicator for corticosteroids responsiveness, and a cutoff < 25 ppb for unresponsiveness [14]. FeNO seems to be also affected by other drugs efficacious for the treatment of chronic cough, such as anti-leukotriene agent especially in association with inhaled steroids [63,64], but not by phosphodiesterase inhibitors [65].

Nasal NO provided a valuable noninvasive, objective measure of the response to therapy in patients with chronic RS and abnormal CT scan [66].

9. Conclusions

Chronic cough poses diagnostic and therapeutic challenges to clinicians, and accurate diagnosis is often not easy. Although several conventional tests such as spirometry, methacholine challenge, bronchodilator responsiveness are commonly used in the diagnosis, FeNO and

nNO measurements might evaluate different aspects of the diseases causing chronic cough. In some studies, the combined use of several methods (*e.g.*, FeNO, blood eosinophils and spirometry), have provided better information than the single methods [18,67].

NO determination is non-invasive, does not require drug administration and, having a high positive predictive power, may help in decision making concerning subsequent steps in the diagnostic evaluation of patients with chronic cough. FeNO levels are increased in asthma, cough variant asthma, and non-asthmatic eosinophilic bronchitis. Thus, the utility of FeNO determination relies more in defining a subgroups of subjects among those with chronic cough than on the definitive diagnosis of chronic cough itself.

Finally, most studies suggest that NO measurement might identify patients with ICS-responsive chronic cough, although more clinical studies are needed to support this conclusion.

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