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Fractional Exhaled Nitric Oxide Testing: Change in Clinical Management of Asthma, or Chronic Obstructive Pulmonary

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ABSTRACT

Asthma and chronic obstructive pulmonary disease (COPD) are common airway inflammatory conditions that can present in isolation or a combination known as asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS). Due to similarities in clinical presentation, differentiating these conditions can be challenging. Fractional exhaled nitric oxide (FeNO) is an endogenous molecule that can be elevated in patients with airway inflammation, particularly asthma. The purpose of this study was to determine if FeNO levels can be used to change pharmacologic management (addition, in patients presenting with asthma, COPD, and ACOS. A retrospective chart review of 250 patients underwent FeNO testing; 93 patients were included in the final analysis with their FeNO levels and medications. Out of 76 patients, 34 were prescribed medications of interest (inhaled corticosteroids (ICS), Inhaled corticosteroids - long-acting beta-agonists (ICS-LABA), anticholinergics (AC) monotherapy or combination therapy). After the FeNO testing, the number of patients on ICS therapy doubled (8 to 16), and the number of patients on ICS -LABA increased by 69.2%. Lastly, the number of patients not on medication of interest, 57.1%, ended up on one after FeNO testing. Our results support the utility of FeNO as a viable test to manage patients with obstructive lung disease.

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are chronic inflammatory airway conditions that present with airflow limitation, often leading to shortness of breath. These can present as unique conditions and a combination known as asthma–chronic obstructive pulmonary disease overlap syndrome (ACOS). ACOS is a commonly encountered yet poorly defined condition due to insufficient clinical data and complex clinical presentations. Literature suggests that patients with features of both typically carry a worse prognosis than individuals with asthma or COPD alone. Patients with this combination are more likely to experience exacerbations, rapidly declining lung function, and a higher mortality rate. Data suggests that about 15% of adults are affected by this condition in the United States, contributing to more than 15 million lost workdays [1,2]. Current projections suggest that COPD will become the leading cause of death worldwide in 15 years [3].

Fractional exhaled nitric oxide (FeNO) is a non-invasive breath test that measures nitric oxide levels and endogenous gaseous molecules. Nitric oxide (NO) levels increase during airway inflammation and can be used to identify allergic/eosinophilic inflammation. One of the key benefits of this test is that it helps identify patients who are likely to respond positively to steroids; predictability is more consistent than spirometry, peak flow, airway hyperresponsiveness to methacholine, and bronchodilator. In addition to improved predictability, it can be used in detecting eosinophilic airway inflammation, monitoring airway inflammation, and possible nonadherence to steroid therapy [4]. Asthmatics tend to produce higher levels of nitric oxide that can be measured using the FeNO test. FeNO levels of < 25 of parts per billion (ppb), 25 ppb – 50 ppb, and > 50 ppb are considered as normal, intermediate, and high, respectively [4].

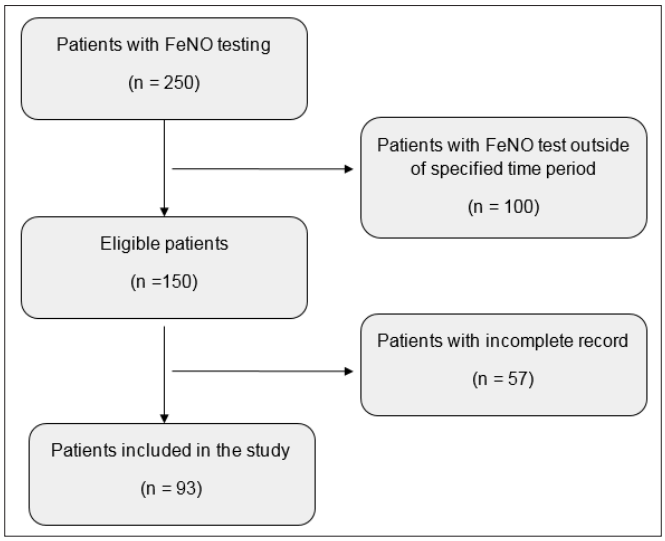
The purpose of this study was to determine if FeNO levels can lead to a change (addition, discontinuing, or change) in the pharmacologic management of patients with asthma, COPD, and ACOS. For the purposes of this study, our management focused on inhaled corticosteroids (ICS), Inhaled corticosteroids - long-acting beta-agonists (ICS-LABA), anticholinergics (AC) monotherapy, or combination therapy.

Materials and Methods

We reviewed the records of all the FeNO tests performed between November 1, 2016, and February 2018, in our outpatient clinic and at affiliated hospitals. We identified 250 patients who met the inclusion criteria; therefore, their electronic medical records (EMR) were obtained and evaluated. Out of 250 patients, 100 were eliminated since their FeNO results were outside of our specified time period. Furthermore, we excluded 57 patients with incomplete data (Figure 1).

Subsequently, their age, race, date of birth, medical record number, presenting symptoms, pulmonary medications, pulmonary function test (PFT) results, FeNO levels, and smoking history. Subsequently, NIOX values, along with their pre and post diagnoses, were entered into an electronic spreadsheet (Microsoft Excel, Microsoft Office, Redmond, Washington). The number of patients on mono or combination therapy was recorded, followed by calculating the mean and the range of FeNO (ppb) levels. Next, the number of patients without medication(s) of interest, their collective mean and range of FeNO (ppb) levels were determined, followed by identifying the number of patients whose therapeutic management changed based on FeNO (ppb) levels. Change in medical management was recorded, followed by noting their FeNO levels.

Figure 1: Study flow chart of patients in this study



FeNO: fractional exhaled nitric oxide

Results

Our analysis included patients who underwent FeNO testing between November 1st, 2016, to February 28th, 2017. For the purpose of simplicity, medical management options were restricted to inhaled corticosteroids (ICS), Inhaled corticosteroids - long-acting beta-agonist (ICS-LABA), and anticholinergics (AC) prescribed as monotherapy or as combination therapy.

Although not the primary focus of this study, the cohort of patients under evaluation was categorized with asthma, chronic obstructive pulmonary disease (COPD), and asthma-COPD overlap syndrome (ACOS). Diagnosis of chronic bronchitis and emphysema was nested under the diagnosis of COPD.

A total of 93 patients were included in this study. Before FeNO testing, 8, 13, and 8 patients were prescribed ICS, ICS-LABA, and AC, respectively. The mean FeNO (ppb) level in patients on ICS, ICS-LABA, and AC were 62.2 (ppb), 39.5 (ppb), and 24.5 (ppb), respectively (Table 1). In addition to monotherapy, combination therapy usage was noted along with relative FeNO levels (ppb). Our analysis revealed that 42 patients were not on mono or combination therapy, and their mean FeNO levels were recorded as 19.7 (ppb).

Table 1: Medications before FeNO testing

Medication(s)	No. of Patients (total =76)	Mean FeNO (ppb)	FeNO (ppb) range
ICS only	8	62.2	14 – 179
ICS – LABA only	13	39.5	5 – 204
AC only	8	24.5	7 – 51
ICS and ICS – LABA	3	28.6	10 – 46
ICS, ICS - LABA, and AC	2	12	8 - 16
Not on ICS, ICS - LABA, AC, or combination	42	19.7	5 - 89
*17 patients on medications other than ICS, ICS - LABA, or AC			

FeNO: fractional exhaled nitric oxide; ppb: parts per billion; ICS: inhaled corticosteroids; ICS - LABA: inhaled corticosteroids - long-acting beta-agonist; AC: anticholinergics After FeNO testing, 16 patients were prescribed ICS, 22 patients prescribed ICS-LABA, and five on AC, respectively. The mean FeNO (ppb) levels in patients on ICS, ICS-LABA, and AC were 44.3 (ppb), 23.4 (ppb), and 10.8 (ppb), respectively (Table 2).

Table 2: Medications after FeNO testing

Medication(s)	No. of patients (total =73)	Mean FeNO (ppb)	FeNO range (ppb)
ICS only	16	44.3	13 - 179
ICS – LABA only	22	23.4	5 - 89
AC only	5	10.8	5 - 18
ICS + ICS – LABA only	3	107.3	12 - 204
ICS + ICS - LABA + AC	1	79	N/A
Not on ICS, ICS - LABA, AC or combination	26	19.5	5 - 96

FeNO: fractional exhaled nitric oxide; ppb: parts per billion; ICS: inhaled corticosteroids; ICS - LABA: inhaled corticosteroids - long-acting beta-agonist; AC: anticholinergics

There were a total of 42 patients (Table 1) who had not been prescribed any medications prior to the FeNO test; however, 24 of the 42 patients were prescribed medication(s) after the testing (Table 3), and 18 were not prescribed any medication after the FeNO test (Table 4). It is important to note that 24 patients were prescribed medication, six were prescribed ICS, and 11 were added to the combination regimen.

Table 3: Change in medication status (No medication pre-FeNO to individual or combination therapy post FeNO)

FeNO (ppb)			
Medication(s)	**Number of patients**	**Mean (ppb)**	**Range (ppb)**
ICS only	6	20.1	13 - 28
ICS – LABA only	11	26.9	5 – 89
AC only	2	9.5	5 – 14
ICS + ICS – LABA	1	12	N/A
ICS + AC	2	29.5	28 – 31
ICS – LABA + AC	2	16	15 – 17
Total number of patients = 24 Mean FeNO and range (ppb): 22.5, 5 – 89			

FeNO: fractional exhaled nitric oxide; ppb: parts per billion; ICS: inhaled corticosteroids; ICS - LABA: inhaled corticosteroids - long-acting beta-agonist; AC: anticholinergics

Table 4: Total number of patients without medications after FeNO test

No. of patients	Mean FeNO (ppb)	FeNO range (ppb)
18	15.9	5 - 60

FeNO: fractional exhaled nitric oxide; ppb: parts per billion

Patients whose post FeNO management included change of pharmacologic agent to ICS (n=14) were diagnosed with asthma only (n=6, mean FeNO 52.1 ppb), COPD only (n=1 mean FeNO 25 ppb), ACOS (n=7, mean FeNO 42.2 ppb).

Patients with a change in management following the FeNO test (no ICS no ICS-LABA to ICS or ICS-LABA) carried the diagnosis of asthma only (n=5, mean FeNO 21.8 ppb), COPD only (n=1, mean FeNO 25 ppb), and ACOS (n=2, mean FeNO 34.5 ppb).

Discussion

Asthma and COPD are obstructive conditions that target small airways leading to airflow limitations, mucus production, and bronchoconstriction. Asthma affects the airways, while COPD affects the airways and parenchyma. One of the most important differences between these two conditions involves the type of inflammation. Asthma is an eosinophilic and CD4-driven inflammatory change, while COPD is driven by neutrophilic and CD8 cells [5,6].

Inhaled steroids are effective against eosinophilic asthma inflammation but not against neutrophilic seen in COPD [7]. There is ample evidence that most patients, not all, with asthma can experience airway remodeling leading to partially reversible airway obstruction [8]. Some patients with long-standing asthma can present irreversible obstruction, which generates a partial response to SABA and or steroids. It is not uncommon to evaluate patients with characteristics of both conditions. Similarities in clinical manifestations provide a challenge in reaching an accurate diagnosis to avoid delays in care. FeNO is a simple and noninvasive test determining the production of the endogenous inflammatory marker, nitric oxide that can be valuable for healthcare providers to render appropriate and timely management [9].

In our cohort, eight patients with the diagnosis of asthma and or COPD were treated with ICS monotherapy (Table 1). However, after the FeNO test, the number of patients on ICS doubled from 8 to 16 with a mean FeNO of 44.3 ppb. This falls near the upper limit of the intermediate-range (Table 2). Further breakdown of the patients on ICS therapy after the testing revealed that 11 out of 16 patients had a diagnosis of asthma with a mean FeNO level of 52.1 ppb. Five patients managed with ICS therapy had a mixed diagnosis of ACOS (mean FeNO 42.5 ppb).

The number of patients on combination therapy of ICS-LABA increased by 69.2% (n=13 to n=22) with a mean FeNO of 23.4 ppb. In this subgroup, 14 patients were identified as asthmatics, two as COPD, and five as ACOS with a mean FeNO of 30.6 ppb, 17 ppb, and 49.3 ppb, respectively.

Prior to FeNO testing, 42 patients diagnosed with asthma, COPD, or ACOS were not prescribed ICS, ICS-LABA, AC, or combination therapy and were managed appropriately according to their FeNO levels [10]. These patients had mean FeNO levels of 19.7 ppb fall in the normal range [11]. Implementation of the FeNO testing led to a change in their management which reduced the number of patients without medications from 42 to 18 (a decrease of 57.1%). In a recent systematic review and meta-analysis that included a total of 175 studies, the results revealed that FeNO results increased odds of correctly diagnosing asthma by 5.85 to 16.95 folds [12].

In addition to appropriate management, FeNO testing is cost-effective. A recent Swedish study determined that using FeNO testing in asthma management led to saving SEK 672, Swedish currency, per patient, which translates to savings of 78.2 USD per patient [13].

Limitations in this study may include an inaccurate diagnosis prior to performing FENO. Mixed restrictive lung disease and other concomitant pulmonary, neurologic, cardiovascular, and rheumatologic diseases may obscure the original clinical picture. Even though NIOX has been shown in some studies to lead to a change in diagnosis, this may be obscured by imprecise history taking or technical failure in testing [14].

Conclusion

FeNO testing is an affordable outpatient tool that can be added to other clinical criteria and tests to help manage patients with obstructive lung disease. Even though it is most helpful when deciding which medication to give an asthmatic, it often leads to a change in management of COPD or ACOS, as well. Optimal therapy may include adding medications and, in some cases, removing agents that may not be of clinical benefit and potentially increasing the risk of adverse reactions or symptoms.

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