Original Article

The Value of Fractional Exhaled Nitric Oxide and Forced Mid-Expiratory Flow as Predictive Markers of Bronchial Hyperresponsiveness in Adults With Chronic Cough

Wuping Bao, MD[a,*], Xue Zhang, BMed[a,*], Chengjian Lv, BS[a,*], Luhong Bao, BS[a], Junfeng Yin, PhD[b], Zhixuan Huang, BS[b], Bing Wang, BMed[a], Xin Zhou, MD[a], and Min Zhang, MD[a] *Shanghai, China*

What is already known about this topic? Small-airway dysfunction contributes to the pathophysiology of even the mildest forms of classical asthma. It may exist in cough-variant asthma, and its presence could be helpful in predicting bronchial hyperresponsiveness (BHR).

What does this article add to our knowledge? Small-airway dysfunction is present in patients with chronic cough and BHR. Forced expiratory flow between 25% and 75% ($FEF_{25\%-75\%}$) can be used to predict BHR when combined with fractional exhaled nitric oxide (FENO).

How does this study impact current management guidelines? FENO > 43 ppb and $FEF_{25\%-75\%}$ < 78.5% strongly predicted positive BHR in Chinese patients. This method is more accessible and convenient than bronchial provocation tests, especially for doctors in primary hospitals.

BACKGROUND: Bronchial provocation tests are standard for diagnosing the etiology of chronic cough, but they are time consuming and can induce severe bronchospasm. A safer and faster clinical examination to predict bronchial hyperresponsiveness (BHR) is needed.

OBJECTIVE: The objective of this study was to investigate whether small-airway function tests can predict BHR in adult patients with chronic cough.

METHODS: A retrospective, cross-sectional study of diagnoses made using spirometry and bronchial provocation test results was performed in 290 patients with chronic nonproductive cough. BHR-predictive values were analyzed via the area under receiver operating characteristic curves (AUCs). Optimal cutoff values were determined by maximizing the sum of sensitivity and specificity.

RESULTS: Patients with chronic cough with BHR showed lower forced expiratory flow between 25% and 75% ($FEF_{25\%-75\%}$), higher fractional exhaled nitric oxide (FENO), and a higher percentage of eosinophils in blood than patients without BHR ($P < .0001$ for all). The AUCs of FENO and $FEF_{25\%-75\%}$ for a BHR diagnosis were 0.788 (95% CI, 0.725-0.851) and 0.702 (95% CI, 0.641-0.763), respectively. Optimal cutoff values were 43 ppb for FENO and 78.5% for $FEF_{25\%-75\%}$, with negative predictive values of 85.38% and 81.34%, respectively. The combined use of FENO and $FEF_{25\%-75\%}$ increased the AUC to 0.843 (95% CI, 0.794-0.892), significantly higher than either FENO ($P = .012$) or $FEF_{25\%-75\%}$ ($P < .0001$) alone.

CONCLUSIONS: Small-airway dysfunction is present in patients with chronic cough and BHR. $FEF_{25\%-75\%}$ has value as a negative predictive parameter for BHR, especially when combined with FENO. FENO > 43 ppb and $FEF_{25\%-75\%}$ < 78.5% strongly predicted a positive bronchial provocation test. **(J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *Asthma diagnosis; Fractional exhaled nitric oxide; Small-airway function; Bronchial provocation; Cough*

Chronic cough (>8 weeks) is one of the most frequent complaints in pulmonary outpatient clinics and severely impairs patients' quality of life. Cough-variant asthma (CVA), first reported by Stanescu and Teculescu in 1970[1] and subsequently named by O'Connell et al in 1991,[2] is one of the most frequent causes of chronic cough[3-6] in adult nonsmokers, accounting for 24% to 29% of chronic cough. CVA is diagnosed on the basis of chronic cough that responds to bronchodilators and the presence of bronchial hyperresponsiveness (BHR),[3-7] which is traditionally demonstrated by performing bronchial provocation tests such as

[a]Department of Respiratory Medicine, Shanghai General Hospital, Shanghai Jiao Tong University, Shanghai, China
[b]School of Mathematical sciences, Tongji University, Shanghai, China
This work was financially supported by grants from the National Natural Science Foundation of China (Grant No. 81470218).
Conflicts of interest: The authors declare that they have no relevant conflicts of interest.
Received for publication June 20, 2017; revised September 11, 2017; accepted for publication September 22, 2017.
Available online ■■
Corresponding author: Min Zhang, MD, and Xin Zhou, MD, Department of Respiratory Medicine, Shanghai General Hospital, Shanghai Jiao Tong University, No. 100, Haining Road, Shanghai 200080, China. E-mail: maggie_zhangmin@163.com.
* These authors contributed equally to this work.
2213-2198

https://doi.org/10.1016/j.jaip.2017.09.026

Abbreviations used

ATS- American Thoracic Society
AUC- Area under the curves
BHR- Bronchial hyperresponsiveness
CalvNO- The alveolar component of fractional exhaled nitric oxide
CVA- Cough-variant asthma
ERS- European Respiratory Society
EOS%- Eosinophils percentages in blood
$EF_{50\%}$- Forced expiratory flow at 50% of forced vital capacity
$FEF_{75\%}$- Forced expiratory flow at 75% of forced vital capacity
$FEF_{25\%}$- Forced expiratory flow at 25% of forced vital capacity
$FEF_{25\%-75\%}$- Forced expiratory flow between 25% and 75%
FENO- Fractional exhaled nitric oxide
FEV_1- Forced expiratory volume in 1 second
FVC- Forced vital capacity
MCH- Methacholine
NLR- Negative likelihood ratios
NPV- Negative predictive values
PD_{20}- Provocative dose of a substance causing a 20% fall in FEV_1
PLR- Positive likelihood ratios
PPV- Positive predictive values
ROC- Receiver operating characteristic

methacholine (MCH) and histamine challenges. Although bronchial provocation tests are considered of great value in confirming or excluding asthma, they are time consuming, expensive, and associated with a small risk of inducing severe bronchospasm. Not all hospitals, especially primary hospitals, perform the bronchoprovocation test. Therefore, clinical examinations that can predict the BHR safely and quickly are needed both for general practitioners and pulmonologists.

Measurement of fractional exhaled nitric oxide (FENO) is widely accepted as a noninvasive biomarker for defining airway eosinophilic inflammation and predicting corticosteroid sensitivity in asthma and other allergic diseases, such as allergic rhinitis. Eosinophilic inflammation is also a key element in the diagnosis and pathogenesis of CVA. FENO values are significantly higher in patients with CVA than in those with chronic cough not attributable to asthma or in healthy volunteers,[8,9] suggesting a potentially useful role for FENO measurement in the etiological diagnosis of chronic cough. Using 30 ppb as the FENO cutoff point, the sensitivity and specificity of FENO for detecting CVA were 75% and 87%, respectively.[8] FENO higher than 33.9 ppb cutoff can positively predict inhaled corticosteroid efficacy for patients with chronic cough.[10] Compared with the bronchoprovocation test, measurement of FENO is extremely easy, quick, and safe to perform.

Asthma is considered a disease predominantly of large airway dysfunction. However, increasing evidence shows that small airways (<2 mm diameter) and surrounding alveolar tissue, traditionally labeled the "quiet zone," are important sites of inflammation and independently contribute to the clinical expression of asthma regardless of asthma severity.[8] Small-airway function is associated with clinical control, asthmatic exacerbation, nocturnal asthmatic attacks, and exercise-induced asthmatic attacks.[11] Importantly, the small airways are involved in BHR. Changes in the small airways measured with oscillometry correlate with symptoms during provocation tests, whereas proximal airways (forced expiratory volume in 1 second [FEV_1], spirometry) do not.[12,13] In addition, more severe BHR was associated with lower forced expiratory flow at 25% to 75% ($FEF_{25\%-75\%}$) of forced vital capacity (FVC), $FEF_{50\%}$, $FEF_{75\%}$, and small-airway inflammation in patients who were matched for FEV_1 percent predicted.[14-18] This evidence suggests that small-airway function might predict BHR when used as a single marker or combined with other measurements.

Spirometry, body plethysmography, single/multiple breath nitrogen washout, forced oscillation technique, prolonged sputum induction, and high-resolution computed tomography are used to assess small-airway function noninvasively. Spirometry is the most easily available and widely used of these methods. $FEF_{25\%-75\%}$ obtained by spirometry is significantly lower in asthmatic patients with near-normal FEV_1 and FVC values than in normal volunteers.[19,20] It may therefore be a possible marker of early bronchial impairment and a more sensitive indicator of small-airway function, particularly in allergic subjects with normal FEV_1, such as those with mild asthma, allergic rhinitis, or CVA.

The aim of this study was to determine the diagnostic value of several noninvasive measures, including FENO and $FEF_{25\%-75\%}$, alone or in combination, in predicting the presence of BHR in patients with chronic cough.

METHODS

Study design and subject selection

We performed a cross-sectional study of diagnostic data from patients with chronic nonproductive cough of at least 2 months' duration who were referred to the Pulmonary Outpatient Clinic of Shanghai General Hospital, Shanghai Jiao Tong University (China) and accepted spirometry and MCH bronchoprovocation tests from June 2016 to December 2016. Patient charts were retrospectively and consecutively evaluated to obtain the detailed clinical history and results of clinical examinations.

Only patients who met all of the following criteria were eligible for study inclusion: history of chronic nonproductive cough, normal chest x-ray or computed tomography results, predicted FEV_1 of 70% or greater with spirometric measurement, and MCH bronchial provocation tests performed.

Patients were excluded if they met the following criteria: respiratory tract infections within 6 weeks before the evaluation, use of inhaled or oral corticosteroid in the previous 4 weeks, or use of montelukast and long-acting β_2-agonists in the previous week.

Descriptive characteristics, clinical history, results of the bronchial provocation test, spirometry, FENO, and percentages of eosinophils in peripheral blood (EOS%) were reviewed and analyzed.

The ethics committee of Shanghai General Hospital, Shanghai Jiao Tong University approved the protocol and a waiver of informed consent was given for our study.

Spirometric measurements

Spirometric assessments were performed with a spirometer (Jaeger, Hoechberg, Germany) in accordance with the specifications and performance criteria recommended in the American Thoracic Society (ATS)/European Respiratory Society (ERS) Standardization of Spirometry.[21] The following spirometric assessments were reviewed: FVC, FEV_1, FEV_1/FVC, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, and $FEF_{25\%-75\%}$. FEV_1, FVC, $FEF_{25\%}$, $FEF_{50\%}$, $FEF_{75\%}$, and $FEF_{25\%-75\%}$ are expressed as percentages of predicted values. FEV_1/FVC is expressed as an absolute value.