

Clinical features in patients of cough variant asthma with normal and high level of exhaled fractional nitric oxide

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Abstract

Objective: Cough variant asthma (CVA) is a subtype of asthma that is characterized by a chronic cough. The clinical characteristics and pulmonary function in patients with CVA who had normal and high exhaled fractional nitric oxide (FeNO) levels were compared.

Methods: The clinical history and pulmonary function data from 99 patients with newly diagnosed CVA were collected.

Result: Newly diagnosed subjects with CVA were divided into a high FeNO group (FeNO value over or equal to 25 ppb, $n = 52$) and a normal FeNO group (FeNO lower than 25 ppb, $n = 47$). There were more patients with coexistent allergic rhinitis or with family histories of allergic diseases in the high FeNO group. More patients in the high FeNO group reported that their chronic cough was triggered by allergen exposure. In the high FeNO group, the patients were younger than in the normal FeNO group. It was shown that baseline lung function tests were normal in all subjects, apart from a reduced midexpiratory flow rate (FEF25-75). There was a significant decrease in FEF25-75 in the high FeNO group compared with the normal FeNO group. No difference was found in the PD20 or the maximal FEV1 drop between the two groups. The multi-factor logistic regression analysis showed that concomitant with allergic rhinitis was the high risk factor of a high FeNO in these subjects with CVA (OR = 5.03, 95% CI, 1.88-13.49).

Conclusion: CVA patients showed heterogeneity according to FeNO level. Patients with high FeNO level are more likely to experience symptoms associated with allergies.

KEYWORDS

allergic rhinitis, cough variant asthma, exhaled fractional nitric oxide, FEF25-75%

Abbreviation: FeNO, fraction of exhaled nitric oxide; LCQ, Leicester cough questionnaire; FEV1, forced expired volume in 1 second; FVC, forced vital capacity; FEF25-75%, forced expiratory flow at 25%-75%; PD20, cumulative dose required to achieve a 20% decrease in FEV1.

Wei Tang and Jun Zhou contributed equally to this work.
All the authors do not have any potential conflicts of interests.

1 | INTRODUCTION

Cough variant asthma is a special phenotype of asthma. According to the national survey on the etiology of chronic cough, the most common cause of chronic cough in China is cough variant asthma (CVA).¹ Until now, CVA has been regarded as a precursor of asthma and has been defined as cough that responds to inhalation of $\alpha\beta$ 2-agonist. Many pathophysiological studies revealed that airway inflammation and hyper-responsiveness were similar between CVA and classical asthma.²

Fractional exhaled nitric oxide (FeNO) is known to be a convenient, sensitive marker that can be measured noninvasively to monitor eosinophilic and Th2 type lower airway inflammation.^{3,4} Levels of FeNO have been found to be elevated in patients with bronchial asthma and cough variant asthma, but not in nonallergic cough.^{5,6}

In clinical practice, we have observed that a significant number of patients with CVA have FeNO values within the normal range. However, to our knowledge, there has been no study comparing the clinical characteristics of patients with CVA who have high and normal FeNO values. In this study, we used 25 ppb as the cut-off value and compared the clinical characteristics and lung function in patients with CVA with high and normal FeNO values.

2 | METHODS

2.1 | Subjects

Consecutively newly diagnosed patients with cough variant asthma were enrolled in the study.⁷ None of the patients had a history of steroid use, and all patients had not used any anti-allergy medication within 24 hours prior to enrollment. The diagnosis of cough variant asthma was based on the method reported by Corrao *et al.* and the Global Initiative for Asthma (GINA) guidelines.^{8,9} The patients with cough variant asthma were referred to our clinic for chronic cough that had persisted for longer than 8 weeks without wheezing or dyspnea. They had no past history of asthma or other respiratory diseases. Wheezes or rhonchi were not audible on chest auscultation even with forced expiration. The subjects all demonstrated normal lung function test except bronchial hyperresponsiveness (BHR) to inhaled histamine (see below for method). Bronchodilators (inhaled beta 2-agonists) were effectively treated their coughs. No other apparent causes of cough were identified, (including a history of upper respiratory tract infection within 4 weeks). Participants did not have any signs or symptoms of postnasal drip or gastroesophageal reflux and had not been taking angiotensin-converting enzyme inhibitors. Chest radiograph results were normal.

This study was approved by the Institutional Review Board of Shanghai Ruijin Hospital. The purpose of the research and experimental protocols was explained to all participants, and their written informed consent were obtained prior to enrollment.

2.2 | Demographic data and clinical history

We collected demographic data, including age and gender from all participants. The clinical history included cough duration, Leicester cough questionnaire (LCQ) score, concomitant allergic rhinitis, and family history of allergic dis-

ease such as allergic asthma, allergic rhinitis, and allergic dermatitis. We also asked the subjects about the cough trigger [if their chronic cough was induced by allergen exposure: we inquired about cough induced by household environmental conditions linked to allergen exposure such as house dust, furry pets, molds or virus or bacterial infections (e.g., cough induced mainly after an upper airway infection)].

2.3 | BHR measurement

Forced expired volume in 1 second (FEV1) and forced vital capacity (FVC) were measured utilizing a computerized spirometer (Master Screen Body, Jaeger, Germany) according to the standardization criteria of the American Thoracic Society. To be eligible for the study, the forced expiratory volume in 1 s (FEV1) was required to be 80% or more of the predicted value.

Bronchial responsiveness was tested using an aerodynamic particle sizer (APS) aerosol provocative system (Master Screen Body, Jaeger, Germany). PD20-FEV1 was measured by an inhalation histamine challenge with different concentrations of histamine (0.03–7.8 mg/mL) delivered by the quantitative aerosol dosimeter of the APS system. Initially, baseline FEV1 was measured using a spirometer 2 minutes after inhalation of a control solution (0.9% saline). Subjects inhaled a histamine aerosol from a nebulizer with tidal breathing whilst wearing a nose clip for 2 minutes. Total inhalations of each concentration were administered, and FEV1 was measured three minutes after each period of inhalation. The test was stopped in the event of a fall in baseline FEV1 of 20% compared with the control inhalation solution. The cumulative dose required to achieve a 20% decrease in FEV1 (PD20) was calculated as the provocative dose of histamine causing a 20% fall in FEV1. AHR was considered to be present in subjects with PD20 values less than 2.2 mg. Subjects received two puffs (200 µg) of salbutamol from a metered dose inhaler following the histamine challenge test.

2.4 | FeNO Measurement

FeNO levels were measured according to the guidelines of the American Thoracic Society (ATS) by the single-breath method (on-line measurement) using a fast response (0.02 s) chemiluminescence analyzer (NOA 280; Sievers Instruments Inc., Boulder, CO). All measurements were made using a mouth pressure of 16 cmH₂O corresponding to an expiratory flow of 50 mL/s. Repeated exhalations were performed to achieve three NO values that agreed at the 5% level. Nitrogen Oxide (NO) concentrations were recorded as the average of these three values. The stability of NO measurement among other NO analyzers was also confirmed.¹⁰

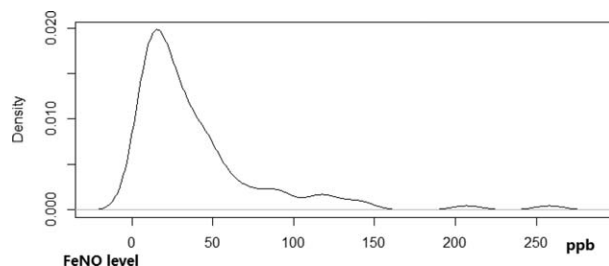


FIGURE 1 Distribution of FeNO level in newly diagnosed CVA patients. FeNO levels were measured in all newly diagnosed CVA patients. Range of FeNO value were from 5ppb to 258ppb. (40.18 ± 42.79 , Means $\pm$ Std)

2.5 | Statistical Analysis

Statistical Package for the Social Sciences (SPSS) statistical software for Windows, Version 19.0 (SPSS Inc, USA) was used for statistical evaluations. Significance level was set as $P < .05$ for all statistical calculations. Continuous variables were expressed as the mean $\pm$ std, while classification variables were expressed as percentages. A T test was used to compare those continuous variables between the normal and high FeNO groups. A multiple factor logistic regression model was used to analyze the influence of those classification variables on the FeNO level.

3 | RESULTS

3.1 | Differences in Demographics and Characteristics of Asthma History Between the High FeNO and Normal FeNO Groups

The subject population consisted of consecutive 99 patients with newly diagnosed cough variant asthma. These patients were randomly enrolled during the investigation period. FeNO levels were from 5 to 258 ppb (Figure 1). According to FeNO level, we divided these CVA subjects into normal FeNO group (FeNO value < 25 ppb)

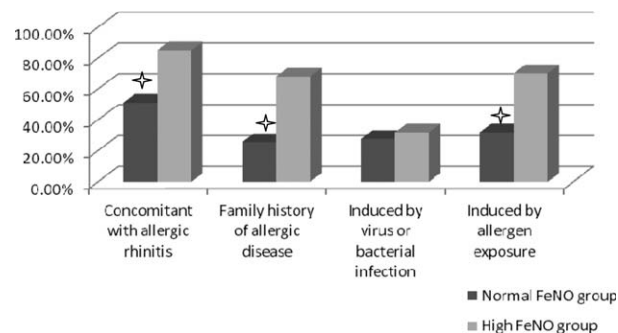


FIGURE 2 Clinical history comparison of CVA patients with normal and high FeNO. *: Compared two groups, $p < 0.05$. According to FeNO level, CVA patients were divided into normal FeNO group and high FeNO group. For taking the medical history, related questions were asked to these CVA patients. The percentage of the subjects admitted related history in each group was shown and compared

and high FeNO group (FeNO value > 25 ppb). The comparison of demographic characteristics in the patients with CVA in normal FeNO and high FeNO group are shown in Table 1. There was no difference in the gender distribution between the two groups. However, in the high FeNO group, the patients were younger than in the normal FeNO group. ($P < .05$).

Comparing the asthma history in the two groups, there was no difference in cough duration or the LCQ score between the high and normal FeNO groups. There were more patients with coexistent allergic rhinitis or with family histories of allergic disease in the high FeNO group compared with the normal FeNO group ($P < .05$). More patients in the high FeNO group reported that their chronic cough was induced by allergen exposure ($P < .05$). In both groups, almost one-third of the patients regarded viral or bacterial infections as induced factors that triggered their cough. The asthma history and clinical characteristics of the two groups are shown in Figure 2.

TABLE 1 Clinical characteristics of patients with CVA with normal FeNO and high FeNO values

Clinical characteristics	Normal FeNO value (FeNO ≤ 25 ppb)	High FeNO value (FeNO > 25 ppb)	P value
Subject number	47	52	NA
FeNO value (ppb) (mean $\pm$ SD)	13.24 ± 5.07	63.89 ± 47.20	$P > .05$
Age (year) (mean $\pm$ SD)	48.43 ± 13.80	32.40 ± 16.48	$P < .05$
Sex (male%)	20 (42.55%)	22 (42.30%)	$P > .05$
Cough duration (months)	4.8 2 (2-18)	5.01 (2-17)	$P > .05$
LSD score	14.42 ± 2.63	14.97 ± 2.25	$P > .05$

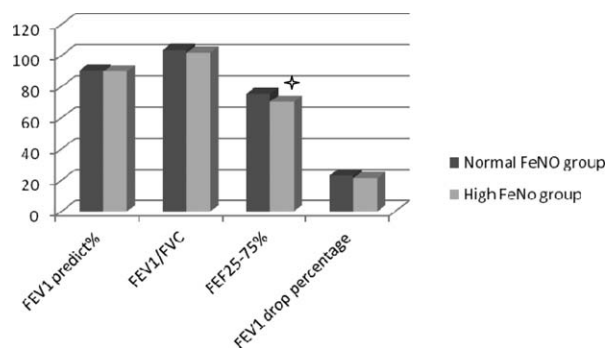


FIGURE 3 Pulmonary function difference in high FeNO and normal FeNO group. ✧: Compared two groups, $p < 0.05$. Lung function test results were compared in the normal and high FeNO group. Lung function criteria included forced expiratory volume in 1 second (FEV1), FEV1/forced vital capacity (FVC) ratio, forced expiratory volume at 25% to 75% (FEF25-75) as well as FEV1 drop percentage after histamine challenge

3.2 | Difference in Pulmonary Function Tests Between the High FeNO and Normal FeNO Groups

We compared the spirometry data from all patients. The baseline lung function tests (including FVC, FEV1, FEV1/FVC) were normal in all subjects with no significant difference between the two groups apart from a reduced mid-expiratory flow rate (FEF25-75) in all the subjects. The FEV1% values in the normal and high FeNO groups were $90.37\% \pm 12.27\%$ and $89.81\% \pm 9.64\%$, respectively ($P > .05$). The FEV1/FVC were $103.52\% \pm 13.85\%$ in the normal FeNO group, and $101.79\% \pm 7.69\%$ in the high FeNO group ($P > .05$). However, there was a slight significant decrease in the FEF25%-75% in the high FeNO group compared with the normal FeNO group ($70.28\% \pm 19.28\%$ vs. $75.34\% \pm 20.39\%$, $P < .05$). No difference was found in the PD20 level (2.46 ± 2.49 in the normal FeNO group and 3.60 ± 7.40 in the high FeNO group, $P > .05$) or the maximal FEV1 drop between the two groups. ($22.97\% \pm 6.80\%$ in the normal FeNO group and $21.28\% \pm 7.03\%$ in the high FeNO group, $P > .05$) (Figure 3).

3.3 | The Influence of Demographic and Clinical Characteristics on FeNO

We used multiple factor logistic regression model in the two groups to analyze the influence of the classification variables on FeNO level, which included age, gender, concomitant allergic rhinitis, family history of allergic disease, and cough induced by allergen exposure or infection. Concomitant allergic rhinitis was the only high risk factor for a high FeNO in these subjects with CVA (OR = 5.03, 95% CI, 1.88-13.49, $P < .05$).

4 | DISCUSSION

Asthma is a heterogeneous disease. From the point view of airway inflammation, there are different phenotypes of asthma, such as eosinophilic, neutrophilic, mixed cell type, and paucigranulocyte type.⁹ However, to date, the diagnosis of cough variant asthma is still based upon a typical clinical manifestation and laboratory evidence of airway hyperresponsiveness to nonspecific stimuli (such as methacholine and histamine) in individuals who respond to traditional asthma therapy.⁷⁻⁹ The mechanisms that trigger cough variant asthma and the types of airway inflammation in CVA are not well understood.

Exhaled NO is regarded as a direct biomarker of eosinophil-mediated mechanisms within the airway and provide a direct indication of ongoing eosinophil-driven inflammation in asthma.¹⁰ In patients with CVA, FeNO is regarded as an important complementary tool for both diagnosis and monitoring treatment efficacy.¹¹ However, besides eosinophil, nitric oxide is also constitutively produced by other cell types: for example, endothelial cells and neuronal cells. In the setting of cytokine-driven airway inflammation, many cells such as eosinophils and epithelial cells can increase NO production in part through increased transcription of inducible NOS (iNOS).¹² On the other hand, although CVA is defined as a variant form of asthma that presents solely with coughing, there are some patients with CVA that have high numbers of neutrophils both in the airway mucosa and in induced sputum.¹³ In our study, although we did not conduct a differential cell count in induced sputum, Japanese researchers have demonstrated the existence of variant sputum cell-subtype profiles in patients with CVA. In this latter study, 32% of 88 subjects with CVA exhibited an eosinophilic profile, 35% neutrophilic, and the remaining paucigranulocytic profiles.¹³ And as we know patients with neutrophilic and paucigranulocytic airway inflammation presented with normal FeNO.¹⁴ Our data was quite consistent with this which showed approximately half of CVA patients were in the normal FeNO group. More recently, in a real life study, it was shown that a significant proportion of unselected asthma patients had normal FeNO levels despite having AHR to mannitol.¹⁵ These data as well as ours suggest that in patients with CVA, eosinophil inflammation is not the sole dominating factor. Rather, other types of airway inflammation likely contribute to the pathogenesis of CVA and cause different FeNO levels, which is consistent with the heterogeneity of typical asthma.

In our study, the level of FeNO showed obvious individual differences in the high FeNO group (from 25 to 258 ppb, Figure 1). This was consistent with data previously published that in patients with CVA, the FeNO was higher than in those with eosinophilic bronchitis.¹⁶ In another study there were significant correlations between the percentage of FeNO

decrease and the percentage of sputum eosinophil decrease or the cough symptom score decrease after ICS therapy.⁴ We believe that in patients with CVA, similar to typical bronchial asthma, except the inhaled corticosteroid sensitive phenotype, there are probably more phenotypes of the disease that may require the development of additional treatment options.

In our study, patients in the high FeNO CVA group had a higher incidence of coexistent allergic rhinitis and/or with a family history of allergy. Those patients in the FeNO high group reported that their symptoms were more likely to be induced by allergen exposure. This finding is consistent with results from numerous studies that reported higher FeNO levels in allergic than non-allergic subjects, in both children and adults.^{17,18} Furthermore, a previous study found that perennial allergic rhinitis was associated with high FeNO levels and more severe asthma.¹⁹ In our study, the subjects were younger in the high FeNO group compared with the normal group, which may be due to a higher prevalence of allergies in younger compared with the older age groups. However, in normal adults, age-related variations in FeNO data are inconsistent.²⁰

Numerous studies have shown that in individuals with asthma, increased FeNO levels are associated with eosinophilia in the blood, sputum, bronchoalveolar fluid and airway mucosa.^{3,4} Concomitant perennial allergic rhinitis has also been associated with higher FeNO levels and a higher percentage of eosinophils in the sputum and blood of patients with classic asthma and has also been linked to increased asthma severity. FeNO levels also correlated with a higher percentage of eosinophils in the sputum of patients with CVA.²¹ These observations indicate that high FeNO levels are related more severe eosinophil infiltration in the airway. In our study, using FEF25-75 as the indicator, the subjects with CVA and high FeNO levels exhibited relatively lower small airway function compared with subjects with normal FeNO levels. This may be due to the impact of higher eosinophilic infiltration in the airway resulting in more severe asthma and pathophysiological damage in patients with CVA. In accordance with this observation, patients with allergic rhinitis have been found to have slightly reduction in FEF25-75 when compared with patients with non-allergic rhinitis.²² To identify the inflammation subtype of patients with CVA with different FeNO levels will require more detailed investigations that include pathologic analysis of induced sputum or bronchoscopic specimens in the future.

5 | CONCLUSION

In our study, patients with CVA showed different levels of FeNO. This reflects one aspects of the heterogeneity of CVA. CVA subjects with high FeNO levels were younger, more likely to have concomitant allergic rhinitis compared with patients with normal FeNO levels. CVA patients in the

high FeNO group also demonstrated a slightly reduction in small airway function.

CONFLICT OF INTERESTS

All the authors do not have any potential conflicts of interests.

AUTHOR CONTRIBUTIONS

Wei Tang and Guo Cao Shi conceived and designed the study; Jun Zhou and Li Li Miao performed experiments; Wei Tang and Jun Zhou analyzed data; Wei Tang and Guo Cao Shi interpreted results and prepared figures; Wei Tang drafted manuscript; Guo Cao Shi edited and revised manuscript; Wei Tang, Jun Zhou, Li Li Miao and Guo Cao Shi approved final version of manuscript.

ETHICS

This study was approved by the Institutional Review Board of Shanghai Ruijin Hospital. The purpose of the research and experimental protocols was explained to all participants, and their written informed consent were obtained prior to enrollment.

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