Clinical utility of ultrahigh fractional exhaled nitric oxide in predicting bronchial hyperresponsiveness in patients with suspected asthma

Jiaxing Liu,[1] Rong Xu,[1] Chen Zhan,[1] Wei Luo,[1] Kefang Lai,[1] Nanshan Zhong,[1] Wei Chen,[2] Ruchong Chen[1]

[1]Department of Respirology, State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China
[2]Department of Biostatistics, Department of Pediatrics, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Correspondence to
Dr Ruchong Chen, Respirology, State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510120, China; chen_rch@163.com

Received 16 December 2018
Revised 18 May 2019
Accepted 23 June 2019

Check for updates

© Author(s) (or their employer(s)) 2019. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Liu J, Xu R, Zhan C, *et al*. *Postgrad Med J* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/postgradmedj-2018-136333

ABSTRACT

Background Fractional exhaled nitric oxide (FeNO) is a non-invasive biomarker for airway eosinophilic inflammation. However, the clinical value of ultrahigh FeNO (≥100 parts per billion (ppb)) in predicting asthma is never explored. We aimed to investigate the value of ultrahigh FeNO as a predictor of bronchial hyperresponsiveness (BHR), an important index for asthma diagnosis.

Methods A retrospective cohort study was conducted on 259 patients with suspected asthma who received the examination of FeNO, spirometry, bronchial provocation test (BPT) and differential cell count of induced sputum. Patients were stratified by FeNO value: ultrahigh (group A:≥100 ppb), high (group B: 50–99 ppb), intermediate (group C: 26–49 ppb) and normal (group D:≤25 ppb). The positive rates of BPT and sputum eosinophils percentage (Eos%) were compared among four cohorts. The correlations between FeNO and sputum Eos% were measured.

Results A significant higher positive rate of BPT was observed in group A (90.91%) than all others (B: 51.43%, C: 31.43%, D: 28.13%, all p<0.01). Referring to group D, the ORs of positive BPT in groups A, B and C were 26.84, 2.84 and 1.05. Sputum Eos% in group A (19.75 (7.00, 46.25)) is higher than that in others (B: 3.50 (1.00, 12.75), C: 1.13 (0.06,3.50), D: 0.50 (0.00, 2.13)). FeNO correlates with sputum Eos% in groups A and B, but not group C or D.

Conclusions Ultrahigh FeNO correlates with BHR and could serve as a practical alternative to methacholine challenge to support an asthma diagnosis in patients with suspected asthma in primary care.

INTRODUCTION

Exhaled nitric oxide (NO), first presented in 1991, is an endogenous gas molecule existing in human and animal exhaled air.[1] NO is produced by the airway epithelial cells and various inflammatory cells when intracellular NO synthase (NOS) increase.[2] The physiological functions of NO in airway include nerve transmission, dilatation of blood vessels, relaxing airway and regulating inflammatory mediators.[3] During the past two decades, fractional exhaled nitric oxide (FeNO) has been more widely applied for the existence and severity of airway diseases such as asthma in practice as a quantitative, non-invasive, simple, and safe method.[4]

Studies have explored the role of FeNO in the diagnosis, evaluation of management efficacy of airway inflammatory diseases (bronchial asthma, chronic obstructive pulmonary disease, eosinophilic bronchitis, etc).[5–8] Research showed that increased FeNO was observed in asthma while decreased FeNO after treatment of corticosteroid.[9 10] In the management of chronic cough, our previous study found that FeNO of 31.5 parts per billion (ppb) had a sensitivity and specificity of 54.0% and 91.4%, respectively, in predicting corticosteroid-responsive cough (including cough variant asthma, non-asthmatic eosinophilic bronchitis and atopic cough) from chronic cough, with a positive predictive value of 89.3% and a negative predictive value of 60.0%.[11] A randomised placebo-controlled clinical trial showed that FeNO can be used to predict whether patients with non-specific respiratory symptoms might benefit from inhaled corticosteroid (ICS) treatment.[12] In a recent study, FeNO>43 ppb plus forced expiratory flow between 25% and 75%, less than 78.5% were predictive of a positive bronchial provocation test (BPT).[13] American Thoracic Society (ATS) guideline (2011) had pointed out that FeNO greater than 25 ppb combined with reference to the clinical context can prompt the possibility of eosinophilic airway inflammation and FeNO greater than 50 ppb suggests a more possible response to corticosteroids.[4] Latest guideline on asthma by National Institute for Health and Care Excellence (NICE) of England recommended spirometry combined with FeNO greater than 40 ppb in diagnosis of clinically suspected asthma.[14] 2018 Global Initiative for Asthma (GINA) states that FeNO has a moderate correlation with airway eosinophilic inflammation. However, whether FeNO can be used as diagnostic criteria for bronchial asthma remains to be further researched.[15]

Asthma is characterised by chronic airway inflammation, variable expiratory airflow limitation and bronchial hyperresponsiveness (BHR). Therefore, as a valuable method to determine BHR, BPT is considered as a vital reference standard in diagnosing asthma. However, BPT is time-consuming and even carries the risk of bronchospasm. A qualified technician is needed to perform this test so it is hardly available in primary care setting. Diagnosis of asthma may be delayed because of the long waiting time for referral to pulmonologists or general hospital. Fortunately, FeNO provide a non-invasive and easy means to evaluate airway inflammation, another feature of asthma. Recently, studies reported different FeNO

Postgrad Med J: first published as 10.1136/postgradmedj-2018-136333 on 11 July 2019. Downloaded from http://pmj.bmj.com/ on 14 July 2019 by guest. Protected by copyright.

values as the diagnostic cut-off points for asthma, but they are mostly focused on subjects with the intermediate range (25–50 ppb) of FeNO level.[11 16 17] Actually, there are patients with high FeNO (50–100 ppb) or ultrahigh level of FeNO (≥100 ppb) in clinical practice, yet whether the ultrahigh level of FeNO (≥100 ppb) indicates more diagnostic accuracy of BHR has not been reported.

The purpose of our study was to investigate the value of ultrahigh FeNO in relating to bronchial responsiveness and the correlation between FeNO and airway inflammation.

METHODS

Patients

Based on the electronic medical record system of the First Affiliated Hospital of Guangzhou Medical University, patients who visited pulmonary department and performed the complete examinations (including FeNO, spirometry, BPT and induced sputum) were continuously enrolled between January 2017 and October 2017. And those who were consistent with the following inclusion criteria were screened into the retrospective cohort. The inclusion criteria of patients were as follows: (1) age 12–75 years old; (2) experienced symptoms of suspicious asthma, such as wheeze, cough, chest tightness, shortness of breath; (3) a normal chest X-ray; (4) without treatment of inhaled or oral corticosteroid, antihistamines or leukotriene receptor antagonists 7 days before examination and (5) no reported history of smoking or severe disease of other system. Patients eligible for inclusion were assigned to the different groups according to pre-defined FeNO categories described in study procedures until sample size of each group reached the predetermined comparative level. Asthma diagnosis is according to the recommendation described in Chinese National Guidelines on the prevention and treatment of bronchial asthma.[18]

The study was approved by the Ethical Committee of the First Affiliated Hospital of Guangzhou Medical University (No. IRB 2016–52). The requirement for approval and the signed informed consent form were exempted by the institutional review board because the study has no intervening trials and has a retrospective nature.

Study Procedures

The demographic and clinical characteristics of patients were collected, including age, gender, FeNO, spirometry, BPT and sputum cytology. Participants were stratified by the FeNO level: ultrahigh (group A: ≥100 ppb), high (group B: 50–99 ppb), intermediate (group C: 26–49 ppb), normal (group D: ≤25 ppb). The spirometry, positive rate of BPT, cumulative provocative dose of methacholine causing a 20% fall in forced expiratory volume in first second (PD_{20}-FEV_1) and percentages of different cells in sputum were compared among four cohorts. Furthermore, the correlations between FeNO and percentages of eosinophils in sputum were analysed.

Measurements

Fractional exhaled nitric oxide

FeNO was evaluated with NIOX MINO analyzer (Aerocrine, Solna, Sweden) (1 ppb=1×10^{-9} mol/L), followed by the spirometry and methacholine challenge tests, referring to the standard procedure issued by ATS/European Respiratory Society (ERS) recommendations.[19] Subjects were informed to deeply inhale NO-free air following exhalation of air in lung, and then exhale in full via a mouthpiece at a constant flow rate (0.05 L/s) for 10 s.

Spirometry and bronchial provocation test

Spirometry and BPT were performed by Jaeger Master Screen (Germany) in accordance with ATS/ERS recommendation.[20] Force vital capacity (FVC), forced expiratory volume in first second (FEV_1), FVC percent predicted (FVC %pred), FEV_1 percent predicted (FEV_1 %pred) and FEV1/FVC ratio were recorded. Methacholine inhalation challenges were adopted to measure BHR that was defined as a cumulative provocative dose of methacholine causing a 20% fall in FEV_1 (PD_{20}-FEV_1) less than 2.500 mg.

Differential cell count of induced sputum

Sputum was induced and processed as previously described.[21] Subjects were asked to inhale 3% hypertonic saline for 7 min via ultrasonic nebulizer and the same process can be repeated for a second or third 7 min when the expectoration was insufficient. Cell smear and staining with haematoxylin/eosin were prepared for differential counts. In all, 400 non-epithelial cells were counted to record the percentage of neutrophils (Neu), eosinophils (Eos), lymphocytes (Lym) and macrophages (Mac).

Statistical analysis

Data were summarised as numbers and percentages for categorical variables and as median (first and third quartiles) or mean±SD for continuous variables. The association between positive rates of BHR and different categories of FeNO levels was analysed using Pearson's χ^2 test and linear-by-linear association test. Furthermore, logistics regression analysis was employed to evaluate the increased risk of asthma in gradients. Eosinophils percentage (Eos%) and PD_{20}-FEV_1 in each FeNO strata were analysed using Kruskal-Wallis test with a Dunnett post-hoc test. The correlation between FeNO and sputum Eos% was determined by Spearman rank correlation. P value <0.05 was considered statistically significant. All statistical analysis was performed using SPSS V.22.0 (SPSS, Chicago, IL, USA).

RESULTS

Demographics

A total of 259 patients with an average age of 42.09±13.92 (years) were enrolled in this study. Among them, 122 were men and 137 were women, and the male-to-female ratio is 1: 1.12. In all, 123 patients (47.49%) with a positive result on BPTs were finally diagnosed as asthmatics, accompanying the history and response to the treatment. The numbers of subjects in groups A, B, C, and D are 55, 70, 64 and 70, respectively. Clinical data including FeNO, sputum differential cell count and spirometry and PD_{20}-FEV_1 are shown in table 1.

Positive rate of BPT in different groups

The group A (ultrahigh FeNO category) showed the highest positive rate of BPT, and positive rate of BPT decreased progressively from groups A, B, C and D (90.91%, 51.43%, 28.13% and 27.14%, respectively, $p<0.01$ for either χ^2 test or linear-by-linear association test). Compared with all other groups, group A has a significant higher positive rate of BHR (all $p<0.01$). Positive rate of BHR in group B is significantly higher than that in groups C and D ($p<0.05$). There is no statistical difference between groups C and D ($p>0.05$). As for logistics regression analysis of positive rate of BPT, referring to group D, the ORs of groups A, B and C were 26.84, 2.84 and 1.05, respectively.

Postgrad Med J: first published as 10.1136/postgradmedj-2018-136333 on 11 July 2019. Downloaded from http://pmj.bmj.com/ on 14 July 2019 by guest. Protected by copyright.

Table 1 Characteristics of patients in different FeNO categories

	100–300 ppb (A) N=55	50–99 ppb (B) N=70	26–49 ppb (C) N=64	5–25 ppb (D) N=70	P value
Age, years	39.31±13.82	40.56±13.79	45.27±13.10	42.90±14.48	0.09
Male,n (%)*	29 (52.7)	36 (51.4)	30 (46.9)	27 (38.6)	0.35
FeNO, ppb	134(115,158)	61(55,69)	32(29,40)	16(14,21)	<0.001
Sputum Eos, %†	19.75 (7.00,46.25)	3.50 (1.00,12.75)	1.13 (0.06,3.50)	0.50 (0,2.13)	<0.001
Sputum Neu, %†	50.00 (23.00,75.50)	61.50 (35.50,81.88)	74.75 (57.81,90.19)	69.63 (47.88,86.44)	<0.001
Sputum Mac, %†	13.00 (6.00,28.5)	22.00 (6.75,45.00)	17.50 (6.31,31.50)	25.50 (9.38,44.94)	0.20
Sputum Lym, %†	1.50 (0.50,2.60)	1.78 (0.94,3.13)	1.50 (0.75,2.75)	1.63 (1.00,3.00)	0.31
FVC, L	3.77±0.87	3.78±0.94	3.53±0.80	3.46±0.90	0.08
FVC%pred, %	101.47±11.28	101.85±9.97	102.99±14.19	102.75±13.54	0.89
FEV1, L	2.82±0.74	3.00±0.77	2.86±0.69	2.83±0.77	0.47
FEV1%pred, %	89.75±11.57	95.76±10.43	99.59±14.62	99.01±13.09	<0.001
FEV1/FVC, %	75.18±9.51	79.49±8.09	81.30±7.13	81.70±7.52	<0.001
Mch, mg	0.54±0.73	1.58±1.04	2.06±0.81	2.13±0.73	<0.001
PD_{20}-FEV_1, mg†‡	0.12 (0.08, 0.28) (n=50)	0.24 (0.09, 0.89) (n=36)	0.59 (0.23, 0.88) (n=18)	0.88 (0.27, 1.54) (n=19)	<0.001

Data are expressed as mean±SD or number (per cents) or median (first and third quartiles). Data are analysed by one-way analysis of variance, unless otherwise stated.
*Data are analysed using Pearson χ^2 test.
†Data are analysed using Kruskal-Wallis test.
‡Data are only counted in patients with bronchial hyperresponsiveness.
Eos, eosinophils; FEV_1, forced expiratory volume in first second; FVC, force vital capacity;FeNO, fractional exhaled nitric oxide; Lym, lymphocytes; Mac, macrophages; Mch, methacholine; Neu, neutrophils; PD_{20}-FEV_1, cumulative provocative dose of methacholine causing a 20% fall in FEV_1; ppb, parts per billion.

In summary, ultrahigh FeNO (≥100 ppb) represents the greatest likelihood of airway hyperresponsiveness (figure 1).

Percentage of sputum eosinophil (Eos%) and PD_{20}-FEV_1 in different groups

There were differences in the overall distribution of the Eos% in groups A, B, C and D (19.75 (7.00, 46.25), 3.50 (1.00, 12.75), 1.13 (0.06,3.50), 0.50 (0.00, 2.13), p<0.01). Sputum Eos% was significantly higher in group A compared with group B, C or D (all p<0.01). And Eos% of group B is higher than group C (p<0.05) and group D (p<0.01). However, no significant difference was found between groups C and D (p>0.05). PD_{20}-FEV_1 of patients with BHR in group A is lower than that of each other groups (p<0.05) and no differences were observed among groups B, C and D (p>0.05) (table 1, figure 2).

Correlations between FeNO and sputum Eos%

A positive correlation was found between FeNO and sputum Eos% in all subjects (r=0.58, p<0.01), as well as in group A (r=0.30, p<0.05) and group B (r=0.30, p<0.05). However, there was no liner correlation between FeNO and sputum Eos% in group C or D (both p>0.05) (figure 3).

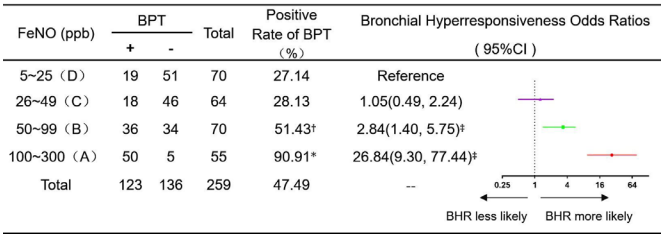

Figure 1 Positive rate of BPT in ultrahigh, high, intermediate and normal FeNO. *Positive rate in ultrahigh FeNO is higher than that of high, intermediate and normal FeNO, all p<0.05. †Positive rate in high FeNO is higher than that of intermediate and normal FeNO, p<0.05. ‡Referring to normal FeNO strata, the ORs of high and ultrahigh FeNO groups are statistically different, p<0.05. BHR, bronchial hyperresponsiveness; BPT, bronchial provocation test; FeNO, fractional exhaled nitric oxide; ppb, parts per billion.

DISCUSSION

Asthma is usually associated with airway hyperresponsiveness that may persist even when symptoms are absent or spirometry is normal.[15] BPT is able to reveal the airway hyperresponsiveness, providing an important reference standard for diagnosing bronchial asthma. However, confirming asthma with BPT meets challenge in primary practice. At present, BPT is mostly performed in the general hospitals or a few specialist clinics, in which it might even take a long time for waiting because of referral or reservation. In primary care setting, the alternative peak expiratory flow (PEF) may partly help to confirm the variable expiratory airflow limitation.[15] However, it requires a good cooperation and adherence. Patients have to test PEF normatively on a routine time in the morning and night everyday over 2 weeks. Bronchial dilation test (BDT) is able to identify reversible airway flow limitation when patients have developed to airway obstruction. However, majority of patients with cough variant asthma and mild asthma have a normal spirometry and those patients could not get a positive BDT result.

There are some other tests for airway inflammation in clinical to help diagnosis and assessment of asthma. Induced sputum test is a pivotal and reliable criterion to differentiate the pattern of airway inflammation, which has been proved to be a non-invasive way to assess the severity and response to ICSs in allergic asthmatics.[22 23] However, it is a time-consuming and labor-dependent examination, and it could be operated only in few respiratory research centres.[24 25] Besides, airway eosinophil inflammation is not a specific index in asthma, also being found in other diseases such as non-asthmatic eosinophil bronchitis (NAEB),[26] eosinophilic granulomatosis with polyangiitis[27] and chronic obstructive pulmonary disease.[28]

In the past two decades, FeNO has been popularised and widely applied in not only specialist clinics but also many general

Postgrad Med J: first published as 10.1136/postgradmedj-2018-136333 on 11 July 2019. Downloaded from http://pmj.bmj.com/ on 14 July 2019 by guest. Protected by copyright.

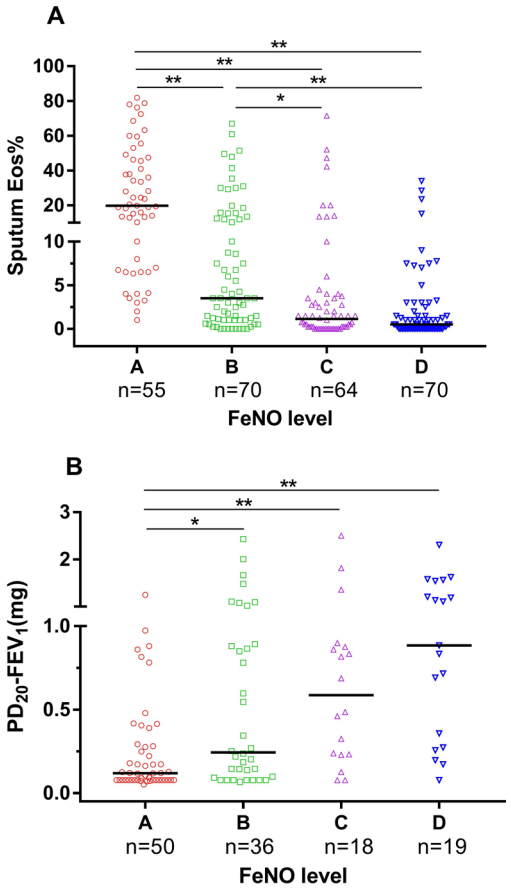

Figure 2 Induced sputum Eos% (A) and PD_{20}-FEV_1 (B) in different FeNO levels. (A) Sputum Eos% in ultrahigh FeNO is higher than that in each other group. Eos% of high FeNO is higher than that of intermediate and normal FeNO groups. However, no significant difference was found between groups C and D (p>0.05). (B) PD_{20}-FEV_1 of ultrahigh FeNO is lower than that of each other group. *p<0.05, **p<0.01. Eos%, eosinophils percentage; FeNO, fractional exhaled nitric oxide; PD_{20}-FEV_1, provocative dose of methacholine causing a 20% fall in forced expiratory volume in first second.

practices in some countries, because of its simple, rapid and non-invasive advantages. ATS guideline (2011) suggested that FeNO is correlated with eosinophilic airway inflammation and

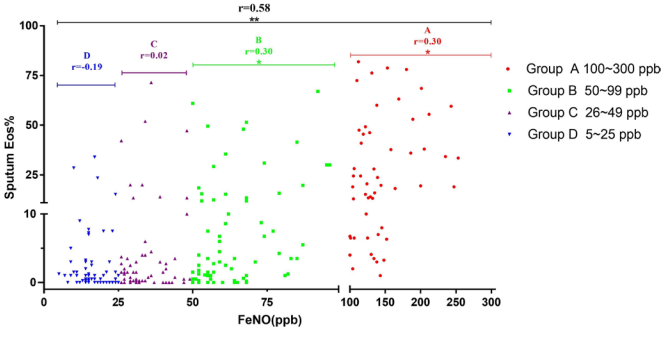

Figure 3 Associations between FeNO and induced sputum Eos%. Positive correlations were found in the whole population, as well as ultrahigh FeNO group and high FeNO group. No significant correlation was found in the intermediate FeNO and normal FeNO group. r=correlation coefficient of spearman rank. *p<0.05, **p<0.01. Eos%, eosinophils percentage; FeNO, fractional exhaled nitric oxide.

may be used to support the diagnosis of asthma in situations in which objective evidence is needed.[4] Latest guideline on asthma by NICE of England recommended spirometry combined with FeNO greater than 40 ppb in diagnosis of clinically suspected asthma.[14] However, GINA (2018) stated conservatively that FeNO had not been established as useful for ruling in or ruling out diagnosis of asthma.[15] This recommendation was based on the existing researches, almost all of which mainly focused on the patients with normal to high FeNO. And the diagnostic cut-off points for asthma are mostly concentrated in the intermediate range (25–50 ppb).[11 16 17] FeNO of these levels may display extensive overlap between asthma and other disease. Actually, there are some patients with a high FeNO (50–99 ppb) or ultrahigh FeNO (≥100 ppb) in clinical practice. Price *et al*[12] had compared the change in Asthma Control Questionnaire 7 after treatment of ICS among patients with different FeNO levels (≤25 ppb, 26–39 ppb, ≥40 ppb), but they did not analyse the patients with ultrahigh FeNO (≥100 ppb) or the difference of BHR among different categories. Whether conclusions are the same in population with ultrahigh FeNO is unknown up to date. To our knowledge, this is the first study focusing on the clinical characteristics of patients with ultrahigh FeNO (≥100 ppb) and how it is associated with BHR.

Our study demonstrated that patients with ultrahigh FeNO are highly likely to be asthmatics. Those patients in ultrahigh FeNO group (90.91% of whom reported BHR) are almost 10 times as likely to present BHR comparing with those in high FeNO (50–99 ppb) category and over 20 times compared with intermediate FeNO category (25–50 ppb). Besides, the lowest PD_{20}-FEV_1 was observed in patients with BHR within ultrahigh FeNO group. This indicated that patients with FeNO ≥100 ppb may present manifestation of airway hyperresponsiveness, which would help diagnosing asthma in general practice and in hospital without BPT. Jatakanon *et al*[29] reported that there was a significant correlation between FeNO and PC_{20}-FEV_1 methacholine (r=−0.64) and Guan *et al*[30] found a similar result in 61 patients with asthma (r=−0.328). But the former only included patients with FeNO lower than 50 ppb and the latter just include few patients with FeNO higher than 50 ppb. Both failed to explore high or ultrahigh FeNO. In our study, 55 patients with ultrahigh FeNO and 70 patients with high FeNO were involved. And a key finding is that positive rate of BHR in patients with ultrahigh FeNO is much higher than all other groups.

By comparing the results of induced sputum Eos% in patients with different levels of FeNO, it was found that airway eosinophilic inflammation was significantly greater in patients with ultrahigh FeNO (median level 19.75%) than those of other FeNO levels. In addition, a higher FeNO was moderately associated with an increased proportion of eosinophils in general (r=0.58). Yune[31] reported a strong correlation (r=0.73) between FeNO and sputum Eos% in 40 patients with clinically suspicious asthma, 70% of whom were ultimately identified as asthma or NAEB. Other studies[8 29 32] showed correlation coefficients ranging from 0.49 to 0.62 in adults with asthma or NAEB. Compared with these studies, our data showed a relatively lower correlation, which may be explained by the difference in population and composition of diseases. Additionally, NO is produced by inducible NOSs, which is upregulated in not only airway epithelial cells and eosinophils but also macrophages, and other inflammatory cells in response to type 2 inflammatory stimulation.[33] Therefore, a moderated correlation between FeNO and sputum eosinophil may be reasonable.

This study had added some new insights on ultrahigh FeNO, but several limitations should be addressed in future. First, due

Postgrad Med J: first published as 10.1136/postgradmedj-2018-136333 on 11 July 2019. Downloaded from http://pmj.bmj.com/ on 14 July 2019 by guest. Protected by copyright.

to the retrospective design without blindness, some potential selection bias may exist though uniform inclusion procedure was established and followed. And clinical diagnostic decision of asthma may be influenced by FeNO levels. Further prospective observations with blind design are merited to be conducted in the future. Second, this study includes only Asian, but not Caucasian or other ethnicity. A study has shown that ethnicity might influence FeNO levels.[34] In some non-Caucasian ethnicities, about 5% of normal healthy children and adults without atopy had FeNO values above the normal Caucasian range.[34] Third, since airway hyperresponsiveness could also be found in a few patients with allergic rhinitis, cystic fibrosis and other condition,[35] the diagnosis of asthma should be based on comprehensive assessment including clinical features, physical examination and laboratory evidence together.

CONCLUSIONS

In conclusion, ultrahigh FeNO is a strong predictor for the BHR, which could serve as a practical alternative to methacholine challenge to support an asthma diagnosis in patients with suspected asthma in primary care where BPT is hardly available. Patients with ultrahigh FeNO are likely to present more obvious eosinophil airway inflammation.

Main messages

- A high positive rate (91%) of bronchial hyperresponsiveness (BHR) was found in patients with ultrahigh fractional exhaled nitric oxide (FeNO; ≥100 parts per billion (ppb)).
- ORs of BHR in patients with ultrahigh FeNO are almost 10 times compared with high FeNO (50–99 ppb).
- Ultrahigh FeNO could serve as a practical alternative to methacholine challenge to support an asthma diagnosis in patients with suspected asthma in primary care where bronchial provocation test is hardly available.

Current research questions

- Due to the retrospective design without blindness, some potential selection bias may exist and clinical diagnostic decision of asthma may be influenced by FeNO levels.
- The conclusion should be validated in other ethnicity except Asian.
- Since airway hyperresponsiveness is not specific for asthma, the diagnosis of asthma should be based on comprehensive assessment.

What is already known on the subject

- FeNO has a moderate correlation with airway eosinophilic inflammation.
- Global Initiative for Asthma stated that FeNO had not been established as useful for ruling in or ruling out diagnosis of asthma, but whether ultrahigh FeNO (≥100 ppb) could identify asthma remained unexplored.
- Further research on clinical utility of ultrahigh FeNO in predicting asthma is need.

Acknowledgements We thank cough lab in the First Affiliated Hospital of Guangzhou Medical University (China) for performance of FeNO and induced sputum test. Also, we appreciate the department of pulmonary function test in the First Affiliated Hospital of Guangzhou Medical University (China) for measuring the spirometry and bronchial provocation test.

Contributors Study concept and design: RC and WC. Data acquisition: JL, RX and CZ. Data analysis: JL, WL, RC and WC. JL, RX and CZ wrote the first draft of the paper, which was then critically reviewed by RC, WC, KL and NZ. All authors read and approved the final manuscript.

Funding This research was partly supported by grants from Incubative Project for Innovation Team of Guangzhou Medical University (2017-159), State Key Laboratory of Respiratory Disease (SKLRD-QN-201702) and National Natural Science Foundation of China (81870079).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (No. IRB 2016-52).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

REFERENCES

1 Gustafsson LE, Leone AM, Persson MG, *et al*. Endogenous nitric oxide is present in the exhaled air of rabbits, guinea pigs and humans. *Biochem Biophys Res Commun* 1991;181:852–7.
2 Kharitonov SA, Barnes PJ. Exhaled markers of pulmonary disease. *Am J Respir Crit Care Med* 2001;163:1693–722.
3 Nathan C, Xie QW. Nitric oxide synthases: roles, tolls, and controls. *Cell* 1994;78:915–8.
4 Dweik RA, Boggs PB, Erzurum SC, *et al*. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* 2011;184:602–15.
5 Price D, Ryan D, Burden A, *et al*. Using fractional exhaled nitric oxide (FeNO) to diagnose steroid-responsive disease and guide asthma management in routine care. *Clin Transl Allergy* 2013;3:37.
6 Chen F-J, Huang X-Y, Liu Y-L, *et al*. Importance of fractional exhaled nitric oxide in the differentiation of asthma-COPD overlap syndrome, asthma, and COPD. *Int J Chron Obstruct Pulmon Dis* 2016;11:2385–90.
7 Donohue JF, Herje N, Crater G, *et al*. Characterization of airway inflammation in patients with COPD using fractional exhaled nitric oxide levels: a pilot study. *Int J Chron Obstruct Pulmon Dis* 2014;9:745–51.
8 Oh M-J, Lee J-Y, Lee B-J, *et al*. Exhaled nitric oxide measurement is useful for the exclusion of nonasthmatic eosinophilic bronchitis in patients with chronic cough. *Chest* 2008;134:990–5.
9 Dupont LJ, Rochette F, Demedts MG, *et al*. Exhaled nitric oxide correlates with airway hyperresponsiveness in steroid-naive patients with mild asthma. *Am J Respir Crit Care Med* 1998;157:894–8.
10 Smith AD, Cowan JO, Brassett KP, *et al*. Exhaled nitric oxide: a predictor of steroid response. *Am J Respir Crit Care Med* 2005;172:453–9.
11 Yi F, Chen R, Luo W, *et al*. Validity of fractional exhaled nitric oxide in diagnosis of corticosteroid-responsive cough. *Chest* 2016;149:1042–51.
12 Price DB, Buhl R, Chan A, *et al*. Fractional exhaled nitric oxide as a predictor of response to inhaled corticosteroids in patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility: a randomised controlled trial. *Lancet Respir Med* 2018;6:29–39.
13 Bao W, Zhang X, Lv C, *et al*. The value of fractional exhaled nitric oxide and forced mid-expiratory flow as predictive markers of bronchial hyperresponsiveness in adults with chronic cough. *J Allergy Clin Immunol Pract* 2018;6:1313–20.
14 National Institute for Health and Care Excellence. Asthma: diagnosis, monitoring and chronic asthma management, 2017. Available: https://www.nice.org.uk/guidance/NG80 [Accessed 15 Sep 2018].
15 Global Initiative for Asthma. Global strategy for asthma management and prevention, 2018. Available: http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/ [Accessed 15 Sep 2018].
16 Wang Y, Li L, Han R, *et al*. Diagnostic value and influencing factors of fractional exhaled nitric oxide in suspected asthma patients. *Int J Clin Exp Pathol* 2015;8:5570–6.
17 Schleich FN, Asandei R, Manise M, *et al*. Is FENO50 useful diagnostic tool in suspected asthma? *Int J Clin Pract* 2012;66:158–65.
18 Asthma Committee of Chinese Thoracic Society. Chinese National Guidelines on the prevention and treatment of bronchial asthma. *Chinese Journal of Tuberculosis and Respiratory Diseases* 2016;39:675–97.
19 American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;171:912–30.
20 Miller MR, Hankinson J, Brusasco V, *et al*. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
21 Pizzichini E, Pizzichini MM, Efthimiadis A, *et al*. Indices of airway inflammation in induced sputum: reproducibility and validity of cell and fluid-phase measurements. *Am J Respir Crit Care Med* 1996;154:308–17.

Postgrad Med J: first published as 10.1136/postgradmedj-2018-136333 on 11 July 2019. Downloaded from http://pmj.bmj.com/ on 14 July 2019 by guest. Protected by copyright.

22 Cowan DC, Cowan JO, Palmay R, *et al*. Effects of steroid therapy on inflammatory cell subtypes in asthma. *Thorax* 2010;65:384–90.
23 Leuppi JD, Salome CM, Jenkins CR, *et al*. Predictive markers of asthma exacerbation during stepwise dose reduction of inhaled corticosteroids. *Am J Respir Crit Care Med* 2001;163:406–12.
24 Efthimiadis A, Spanevello A, Hamid Q, *et al*. Methods of sputum processing for cell counts, immunocytochemistry and in situ hybridisation. *Eur Respir J Suppl* 2002;37:19s–23.
25 Paggiaro PL, Chanez P, Holz O, *et al*. Sputum induction. *Eur Respir J Suppl* 2002;37:3s–8.
26 Brightling CE. Chronic cough due to nonasthmatic eosinophilic bronchitis: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129(1 Suppl):116S–21.
27 Groh M, Pagnoux C, Baldini C, *et al*. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med* 2015;26:545–53.
28 George L, Brightling CE. Eosinophilic airway inflammation: role in asthma and chronic obstructive pulmonary disease. *Ther Adv Chronic Dis* 2016;7:34–51.
29 Jatakanon A, Lim S, Kharitonov SA, *et al*. Correlation between exhaled nitric oxide, sputum eosinophils, and methacholine responsiveness in patients with mild asthma. *Thorax* 1998;53:91–5.
30 Guan W-jie, Shi X, Jiang C-yu, *et al*. Responsiveness to methacholine, but not leukotriene D4, correlates with fractional exhaled nitric oxide in asthma. *Clin Respir J* 2016;10:176–80.
31 Yune S, Lee JY, Choi DC, *et al*. Fractional exhaled nitric oxide: comparison between portable devices and correlation with sputum eosinophils. *Allergy Asthma Immunol Res* 2015;7:404–8.
32 Berry MA, Shaw DE, Green RH, *et al*. The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. *Clin Exp Allergy* 2005;35:1175–9.
33 Nagasaki T, Matsumoto H, Izuhara K, *et al*. Utility of serum periostin in combination with exhaled nitric oxide in the management of asthma. *Allergol Int* 2017;66:404–10.
34 Blake TL, Chang AB, Chatfield MD, *et al*. Does ethnicity influence fractional exhaled nitric oxide in healthy individuals?: A systematic review. *Chest* 2017;152:40–50.
35 Hewitt DJ. Interpretation of the "positive" methacholine challenge. *Am J Ind Med* 2008;51:769–81.

Postgrad Med J: first published as 10.1136/postgradmedj-2018-136333 on 11 July 2019. Downloaded from http://pmj.bmj.com/ on 14 July 2019 by guest. Protected by copyright.