

## Research Article

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# The reliability of adjusting stepped care based on FeNO monitoring for patients with chronic persistent asthma

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**Keywords:** Asthma; FeNO; Reliability; GINA; ACQ score

**Abstract:** Objective: To examine the feasibility of fractional exhaled nitrous oxide (FeNO) guided stepped care in patients with chronic persistent asthma. Methods: 160 patients with asthma were enrolled and randomly divided into study and control groups, and were given standardized treatment according to GINA 2014. All patients were evaluated every 3 months and their medication was adjusted according to the results of evaluation. The control group was adjusted according to the recommended protocol from GINA, while the study group was adjusted on the basis of the control group and combined with the results of FeNO. The complete control rate, failure rate of step-wise treatment, ACQ score, lung function, and peripheral blood eosinophil count were compared between the two groups. Results: In both study and control groups, the patient condition was effectively controlled. Strikingly, the failure rate of step therapy in study group was lower than that of control group ( $P < 0.05$ ), although there were no significant differences between the two groups on total control rate, ACQ score, lung function, and peripheral blood eosinophil count ( $P > 0.05$ ). Furthermore, the levels of FeNO positively correlated with ACQ scores and eosinophil counts or negatively with lung function. Conclusions: The dynamic monitoring of FeNO could effectively guide the medication and reduce the rate of treatment failure, which could be used to inform standardized management of asthma.

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## 1 Introduction

The establishment of airway inflammation theory is the most important progress in the field of asthma research in the past 40 years [1]. The long-term management of asthma patients is based on the standards set by the Global Initiative for Asthma (GINA, 2014) [2], but its control level is based on the improvement of clinical symptoms and lung function in patients without the severity of the chronic airway inflammation [3]. Up to now, the related researches on the feasibility of adjusting asthma medication according to fractional exhaled nitric oxide (FeNO) are limited. Fractional exhaled nitrous oxide (FeNO) is a direct and noninvasive method for monitoring airway inflammation. Previous study has been shown that the continuous application of FeNO could provide more valuable information for the diagnosis and prognosis of patients with asthma [4]. The purpose of the current study is to explore the clinical significance of stepped care for patients with chronic persistent asthma according to the dynamic monitoring of FeNO. Furthermore, we also examine the clinical significance of stepped care for chronic persistent asthma in primary hospitals, and provide clinical evidence for standardized management and further improvement of the total control rate of asthma.

## 2 Materials and methods

### 2.1 Patient selection

#### 2.1.1 Inclusion criteria

(1) The patients met the diagnostic criteria for asthma, according to GINA 2014 [5]; (2) The patients were in the

stage of chronic persistence asthma according to clinical manifestations; (3) The severity of asthma is slightly sustained or above; (4) No inhalation or oral treatment of corticoids within 3 months before admission; (5) The age of the patients were between 18 to 65 years old.

### 2.1.2 Exclusion criteria

(1) Acute respiratory infections within 4 weeks, such as pneumonia, acute and chronic bronchitis, and tuberculosis; (2) Combined with other respiratory diseases, such as chronic obstructive pulmonary disease, bronchiectasis, lung cancer, or in the acute stage of asthma; (3) Severe liver and renal insufficiency and cardiac insufficiency; (4) Pregnant or lactating women; (5) Severe mental disorders; (6) The patients that have other diseases that might impact the results of the current study. (7) Current smokers or former smokers who smoke more than 10 packs /year. (8) This study has been approved by the ethics committee of Shanghai Xuhui Dahua Hospital.

## 2.2 Patients and groups

From January 2016 to December 2017, 160 patients who met the criteria for asthma were enrolled and randomly divided into study and control groups. The two groups were given standardized treatment according to GINA 2014. All patients were evaluated every 3 months, and their medication was adjusted according to the results of evaluation. The control group was adjusted according to the recommended protocol from GINA, while the study group was adjusted on the basis of the control group combined with the results of FeNO. All patients were followed for 1 year. The complete control rate, failure rate of step-wise treatment, ACQ score, lung function, and peripheral blood eosinophil count were compared between two groups.

## 2.3 Intervention

All patients with chronic persistent asthma were treated according to the stepped care protocol recommended by the GINA 2014. The patients were assessed every 3 months. According to the symptoms over the past 4 weeks, medications and lung function tests, the patients were divided into completely controlled, partially control, and uncontrolled. For the control group, according to the proposal of GINA 2014, step-down treatment was performed for com-

pletely controlled patients, and the escalation therapy was performed for partially controlled and uncontrolled patients. The patients in the study group received an assessment of the condition once every 3 months with a FeNO test. Step-down treatment was performed in patients with FeNO < 25 ppb and the complete control of the clinical symptoms. The dose of inhaled corticosteroids (ICS) was doubled for patients with complete clinical control and FeNO  $\geq$  25ppb. In accordance with the recommendations of GINA 2014, patients with partial control and uncontrolled were given step-up treatment, excepting for the factors such as inhalation, compliance, and environmental. If the patient's condition deteriorated during the step-down treatment, the treatment after the downgrade cannot control the condition. Thus, a readjustment to the original treatment program, a higher level of treatment, or hospitalization is required. The study period was 1 year.

## 2.4 Observation Index

### 2.4.1 Clinically controlled rate

The proportion of cases that were completely controlled was recorded at each time point. The clinical criteria are defined in GINA2014. Briefly, there are six criteria. First, patients have no nocturnal symptoms or suffocated to wake up at night. Second, patients have no daytime symptoms or symptoms less than twice per week. Third, daily activities are not restricted and patients can participate in daily activities. Fourth, there is no need to take medications to relieve symptoms or take medications less than twice a week. Fifth, the lung function is close to normal or normal. Sixth, there was no acute attack.

### 2.4.2 Recording of failure rates of staircase step-down

The number of step-down treatments in the two groups and the times of failure after step-down treatments were recorded respectively. The differences in the incidence of the two groups were compared. The definition of downstairs treatment failure is the aggravation of asthma symptoms within 2 weeks after the implementation of downstairs therapy. The failure rate of step-down treatment = the number of times of failure after step-down treatment / the number of steps reduced by 100%.

### 2.4.3 Asthma Control Questionnaire (ACQ)

The patients were correctly assessed and recorded their own condition under the instruction of the same doctor. The ACQ score involved 7 problems, and it was calculated with an average value. The lowest point was 0 and the highest point was 6. The higher the score meant the more severe the symptom of asthma.

### 2.4.4 Determination of FeNO concentration

The FeNO detector, Sunvou-P100, (Share Ltd. Wuxi, China) was used to detect the FeNO. Before testing, the patients were informed the details of the procedure, and the detection of FeNO was strictly followed as per the manufacturer’s instructions. The results were expressed in terms of parts per billion ppb (1ppb=1; 10<sup>-9</sup>mol/L). During expiration, leaking, choking, breathing, and spout saliva must be avoided. The patient cannot smoke, drink alcohol, consume caffeine, and other ingredients on the day of detection. The patient also should not eat high nitrate foods such as broccoli, Gai Lan, lettuce, lettuce, celery, radish, and smoked or pickled food within 3 hours. Severe exercise, lung function tests, or bronchial provocation tests were all prohibited 1 hour before the detection of FeNO. Certain conditions must be recorded, such as the use of corticosteroids and antibiotics for acute infection or fever.

### 2.4.5 Lung function test

According to the ERS standard, the lung function instrument, Quark PFT3, was used (COSMED, Rome, Italy) with the same operator as the FeNO test. The gender, age, height, and weight of patients were entered into the machine, and the expected value was automatically calculated. Severe exercise, inhalation of cold air, smoking, and drinking must be avoided 4 hours before the examination; inhaled corticosteroids, theophylline, beta 2 receptor agonists, and anticholinergic drugs must be stopped 12 hours

before the test. Each patient was measured 3 times. The best 2 mutation rates should not >5% and the best value were kept. FEV1.0% pred, FEV1/FVC%, PEF% PRED and PEF variation rate (ΔPEF%) were recorded.

### 2.4.6 Peripheral blood eosinophil count (EB)

The SysmexHST201 automatic blood cell analyzer was used for direct counting.

## 2.5 Statistical analysis

The statistical analysis was carried out with SPSS18.0, and the data were shown as mean±SD. The differences between the two groups were analyzed by Student’s t test, and the single factor analysis of variance was used among the multiple groups. The data of non-normal distribution were analyzed by c<sup>2</sup> test. Significance was achieved when P< 0.05 for all tests.

## 3 Results

### 3.1 General information

From January 2016 to December 2017, 160 cases of asthma were enrolled, including 80 cases in study group (FeNO test group) and 80 cases in the control group. In the study group, there were 46 males and 34 females with an average age of 40.38±9.85 years, which contained 15 cases of mild persistent patients, 46 moderately persistent cases, and 19 severe persistent cases. In the control group, there were 44 males and 36 females with an average age of 39.67±9.34 years, which contained 13 mild persistent patients, 49 moderate persistent cases and 18 severe persistent cases. There was no significant difference in gender composition, severity distribution, and average age between the two groups, P>0.05. See Table 1.

**Table 1:** General information between two groups.

Group	n	gender		age	severity	
		male	female		mild	moderate
Study group	80	46*	34*	40.38±9.85*	15*	46*
Control group	80	44	36	39.67±9.34	13	49

Note:\*P>0.05

### 3.2 Rate for completely controlled asthma

The proportion of completely controlled patients for the study group was 75.96%, 81.73%, 85.58% and 88.46% at 3 months, 6 months, 9 months and 12 months after treatment respectively and for the control group was 77.67%, 81.55%, 85.44% and 87.38% respectively. There was no significant difference between two groups ( $P>0.05$ ). See Table 2.

### 3.3 Failure rate of step-down treatment

For the entire observation period, there were 183 cases of step-down treatment in the control group, of which 25 cases failed with an incidence of 13.66%. In contrast, there were 151 cases of step-down treatment in the study group, of which 11 cases failed with a statistically significant lower rate of 7.28% ( $P<0.05$ ). See Table 3.

### 3.4 ACQ score

In the study and control groups, the ACQ scores were gradually decreased after standardized treatment, and there was no significant difference in the ACQ scores between the two groups at each time period,  $P>0.05$ . See Table 4

**Table 2:** Rate for completely controlled asthma in the two groups (% , n).

Assess time	Study group	Control group
3 <sup>rd</sup> month	75.96% (79) *	77.67% (80)
6 <sup>th</sup> month	81.73% (85) *	81.55% (84)
9 <sup>th</sup> month	85.58% (89) *	85.44% (88)
12 <sup>th</sup> month	88.46% (92) *	87.38% (90)

Note: \* $P>0.05$

**Table 3:** Failure rate of step-down treatment between two groups.

Group	step-down case	Failed case	Failure rate
Study group	151	11	7.28%#
Control group	183	25	13.66%

Note: # $P<0.05$

### 3.5 Dynamic changes of FeNO concentration in the study group after treatment

After standardized treatment, the FeNO concentrations were gradually decreased in the patients of the study group. The concentrations measured in the third, sixth, ninth and twelfth months were significantly lower than that of those in the initial detection ( $P<0.05$ ). There was no significant difference in concentrations between the sixth, ninth and twelfth months themselves ( $P>0.05$ ). See Table 5.

### 3.6 Lung function

Because the detectable levels of FeNO concentrations were reduced, the lung function of the patients was gradually improved after the standard treatment both in the study and control groups. There was no significant difference between the two groups of FEV1.0% pred, PEF% pred and  $\Delta$ PEF% for each time period,  $P>0.05$ . See Table 6.

**Table 4:** The analysis of ACQ scores between two groups.

Assess time	Study group	Control group
0 months	4.59 $\pm$ 1.07*	4.42 $\pm$ 1.14
3 <sup>rd</sup> month	3.48 $\pm$ 1.06*	3.37 $\pm$ 0.93
6 <sup>th</sup> month	2.16 $\pm$ 0.81*	2.19 $\pm$ 0.89
9 <sup>th</sup> month	1.55 $\pm$ 0.52*	1.68 $\pm$ 0.58
12 <sup>th</sup> month	1.52 $\pm$ 0.56*	1.65 $\pm$ 0.51

Note: \* $P>0.05$

**Table 5:** Dynamic changes of FeNO concentration in the study group after standardized treatment ( $\bar{x} \pm S$ , ppb).

Detection time	Study group
0 months	47.33 $\pm$ 16.58a
3 <sup>rd</sup> month	32.87 $\pm$ 12.42b
6 <sup>th</sup> month	25.32 $\pm$ 10.12c
9 <sup>th</sup> month	24.76 $\pm$ 10.08c
12 <sup>th</sup> month	25.58 $\pm$ 10.72c

Note: <sup>a</sup> $P<0.05$  and <sup>c</sup> $P>0.05$

**Table 6:** Comparison of lung function between the two groups ( $\bar{x} \pm s$ , %).

Detection time	Group	FEV <sub>1,0</sub> %pred	PEF% pred	△PEF%
0 months	Study	71.90±20.33*	70.32±20.25*	20.58±6.32*
	Control	74.34±21.77	73.56±19.21	21.12±6.59
3 <sup>rd</sup> month	Study	79.35±21.57*	78.49±21.08*	16.72±5.09*
	Control	81.17±22.03	79.84±22.81	16.07±5.35
6 <sup>th</sup> month	Study	86.73±22.98*	86.79±23.32*	10.47±3.86*
	Control	85.34±21.67	84.71±21.46	10.41±3.74
9 <sup>th</sup> month	Study	88.06±23.12*	87.37±22.95*	8.11±2.79*
	Control	86.91±21.52	86.42±21.48	8.72±2.44
12 <sup>th</sup> month	Study	89.35±23.68*	89.18±23.10*	7.41±2.30*
	Control	90.12±13.21	91.31±10.85	8.08±2.38

Note: \* $P > 0.05$ .

### 3.7 Peripheral blood eosinophil counts

Consistent with the increased in lung function along with the decreased in FeNO concentration, the eosinophils in the peripheral blood of the patients were gradually decreased both in the study and the control groups. There was no significant difference of peripheral blood eosinophils between the two groups at each time period,  $P > 0.05$ . See Table 7.

## 4 Discussion

Bronchial asthma is a chronic airway inflammatory disease, and the detection and control of airway inflammation is one of the important measures for the management of asthma [6]. So far, accumulated evidence has confirmed that the level of FeNO can reflect the airway inflammation [7] and airway hyper responsiveness [8]. The level of FeNO in the upper respiratory and nasal sinuses of normal people is higher than that in the lower respiratory tract. The epithelial cells in the nose can produce a large amount of NO. The NO in the respiratory tract is mainly from the lower respiratory tract after removing the effect of NO in the nose [9]. NO is produced by nitric oxide synthase (NOS) acting as the substrate of L-arginine. NOS is widely distributed in various tissues of the respiratory system [10]. There are 3 different isozymes, neurogenic NOS, endothelial NOS and inducible NOS (iNOS), which is mainly located in macrophages and epithelial cells [11]. The first two are structural isozymes, while the third has

**Table 7:** Comparison of peripheral blood eosinophil counts between the two groups.

Detection time	Study group	Control group
0 months	0.33±0.12*	0.29±0.13
3 <sup>rd</sup> month	0.25±0.10*	0.23±0.11
6 <sup>th</sup> month	0.14±0.11*	0.13±0.10
9 <sup>th</sup> month	0.13±0.10*	0.13±0.09
12 <sup>th</sup> month	0.12±0.11*	0.12±0.10

Note: all \* $P > 0.05$

high iNOS activity and is not affected by the concentration of calcium ions. iNOS was expressed specifically in the epithelial cells of the respiratory tract, and the expression of iNOS was significantly higher in the asthma patients [12]. The stimulation of inflammatory cytokines in asthmatic patients might increase the expression of iNOS through a variety of mechanisms, resulting in a significant increase in the level of FeNO [13]. After activation by FeNO, eosinophils could secrete a large number of active substances including eosinophilic granules, causing airway epithelial cell damage, airway hyperresponsiveness, chronic airway obstruction and airway inflammation, which are the markers of airway inflammation in most patients with asthma [14, 15]. In accordance with previous reports on FeNO and asthma [16], we observed that over the course of treatment, the reduction of FeNO levels was well correlated with improvement of lung function and decrease in ACQ scores and eosinophil counts.



To date, the adjustment of asthma medication in clinical is mainly guided by the recommendation of GINA, which is based on the number of episodes of patients and the number of acute exacerbations. ACQ is a good monitoring index for the patient's control level in a certain period, and it has a significant negative correlation with lung function. Nevertheless, in clinical practice, we found that cognition and determination of attack and acute exacerbation often had greater deviations between doctors and patients and also among various patients. For instance, because of the differences in tolerance, the attention to the disease, the degree of panic, or symptoms of the same severity might lead to a certain degree of deviation in determining the state of control for doctors. Therefore, more objective and standardized simple method was necessary to help doctors determine the control state of the patient more accurately, so as to achieve better clinical effects and reduce the failure of treatment.

The current study showed that the stepped care guided by FeNO had no significant difference between the study group and the control group with respect to completely controlled rates, ACQ score, lung function and peripheral blood eosinophil count, thus it might reflect the control state of asthma more accurately and comprehensively. Under the guidance of FeNO, patients in the study group had a reduction for the failure rate of step-down treatment compared to the control group, indicating that this index could reflect the status of asthma more accurately. Based on the data, the study group was given less stepped care than the control group (151 vs.183), which might be reflective of a more cautious decision on stepped care after the addition of the FeNO test, which results were informed a regimen that partially avoided treatment failure.

The detection of FeNO is convenient, fast and non-invasive, and it is suitable for large-scale application in the community. The current study showed that the combination of the traditional guidance with FeNO could help physicians adjust the treatment plan more accurately, reduce the failure rate of the stepped care, avoid the recurrence of the illness due to the incorrect treatment of step-down, and better achieve the clinical purpose of asthma control. It has practical clinical significance and advantages. Therefore, it can be used as a good evidence for guiding the standardized management of asthma patients in primary hospitals.

**Competing interests:** The authors' declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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