Original Article

Utility of MostGraph and Fractional Exhaled Nitric Oxide Measurement in Chronic Cough

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ABSTRACT

Background: Patients with chronic cough underwent MostGraph and fractional exhaled nitric oxide (FENO) measurement and pulmonary function testing to determine the effectiveness of these techniques in the differential diagnosis and assessment of treatment of chronic cough.

Methods: This prospective study enrolled 106 adults with chronic cough and 32 patients with stable asthma. Respiratory resistance was measured with the MostGraph-01 device (Chest MI Inc., Tokyo, Japan), FENO was measured with the NIOX-MINO® portable analyzer (Aerocrine, AB, Solna, Sweden), and pulmonary function was evaluated with spirometry. Participants were treated with a combination of β stimulant and inhaled corticosteroid. We compared findings before and after treatment and between patients with chronic cough and asthma.

Results: Airway resistance at 5 Hz (R5) and 20 Hz (R20) tended to be elevated in patients with chronic cough. However, airway resistance and mean FENO significantly decreased during treatment. Pulmonary function tests showed no significant change. Mean FENO was significantly higher among patients with asthma; however, there was no significant difference between patient groups in airway resistance or pulmonary function.

Conclusions: In patients with chronic cough, R5 and R20 were significantly elevated but were lower after treatment. There was no correlation between MostGraph and FENO variables, before or after treatment. Thus, increased airway resistance does not always reflect the extent of eosinophilic inflammation. Our findings suggest that the pathological conditions of stable asthma and chronic cough with eosinophilic inflammations are similar. Combined MostGraph and FENO measurement was quick and noninvasive, and our results indicate that they may be useful in evaluating pathophysiology and treatment effectiveness in chronic cough.

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KEYWORDS: airway resistance at 5 Hz (R5), airway resistance at 20 Hz (R20), chronic cough, fractional exhaled nitric oxide (FENO), MostGraph

An increasing number of patients are presenting with chronic cough, the most frequent underlying causes of which are cough-variant asthma (CVA), nonasthmatic eosinophilic bronchitis (NAEB), gastroesophageal reflux disease (GERD), sinobronchial syndrome, postnasal drip, and cough due to angiotensin-converting enzyme (ACE)

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inhibitors.[1] Much is unknown regarding the pathophysiology of chronic cough, particularly in cases of CVA and NAEB, and differential diagnosis is not always straightforward. Moreover, it is difficult to perform invasive tests on a patient complaining only of cough. Therefore, it is desirable to develop tests that are easy, noninvasive, and lead to quick diagnosis and treatment evaluation on an outpatient basis.

MostGraph and fractional exhaled nitric oxide (FENO) measurement are straightforward, noninvasive tests. In this study, patients with chronic cough underwent MostGraph and FENO measurement and assessment of pulmonary function to evaluate the effectiveness and validity of these techniques in the differential diagnosis and treatment evaluation of chronic cough.

Methods

Patients

From December 2010 through August 2011, 106 adults (34 men and 72 women; mean age, 44 years) were selected from among patients presenting with cough. The inclusion criteria were cough persisting for 8 weeks or longer, without wheezing on auscultation or dyspnea, and absence of abnormalities on chest radiographs. Participants were excluded if they were current smokers; had a history of clinical respiratory tract infection within the previous 8 weeks; were taking ACE inhibitors, steroids, β stimulants, antiallergy drugs, or antihistamines; had clinical sinusitis, postnasal drip, GERD [criteria for GERD: the frequency scale for symptoms of GERD (FSSG)[2]], autoimmune disorder, or sleep apnea; or had a history of clinical heart disease or respiratory disease.

From our outpatient clinic, we recruited 32 patients with stable asthma who were being treated with inhaled corticosteroids at the time of the study. All patients satisfied the definition of asthma of the Global Initiative for Asthma (GINA).

Patients were excluded from the study if they had had any acute viral infection during the 1 month before the study; if they were current smokers, had a smoking history of greater than 10 pack-years, or had quit smoking within the 1-year period before the study; or had chronic obstructive pulmonary disease (COPD).

This study was conducted at the Toho University Ohashi Medical Center and was approved by the Ohashi Hospital Committee (No. 22-21). All participants enrolled in this study provided informed consent (Fig. 1).

Measurements

Blood testing, sputum examination, and chest radiography were performed for differential diagnosis of chronic cough. The blood tests used to screen for infectious diseases included nonspecific immunoglobulin E (IgE) antibodies, mycoplasma immunoglobulin M (IgM) antibodies (IC Act), cold agglutinin titer, pertussis antibodies, and *Chlamydophila pneumoniae* IgM antibodies. Sputum was induced with an aerosol of hypertonic saline from a nebulizer, and the presence of bacteria in sputum was investigated.

Resistance at 5 Hz (R5), at 20 Hz (R20), and R5—R20 were measured by impulse oscillation using the MostGraph-01 (Chest MI Inc., Tokyo, Japan), a device that measures respiratory resistance. Testing was conducted while the participant was seated and wearing a nose clip and mouthpiece while maintaining respiration at a resting level. Because measurement is done at resting respiration, the test was conducted before tests that require forced respiration, such as spirometry. The difference between the inspiratory and expiratory phases and the rate of change were measured for each variable.

Normal values for R5 and R20 have not been established; however, a study of the impulse oscillometry system of normal individuals[3] classified a resistance oscillation frequency of approximately 2 $cmH_2O/l/s$ or less as normal, a value between 2 and 3 $cmH_2O/l/s$ as borderline, and a value of 3 $cmH_2O/l/s$ or higher as highly resistant.[4]

FENO was measured using the NIOX-MINO® device (Aerocrine AB, Solna, Sweden). A mouthpiece was fitted onto seated subjects after peak expiration, and they were asked to exhale at a flow rate of approximately 45 to 55 ml/sec.[5] A sensitivity of 75% and a specificity of 87% were reported when a FENO cutoff of 30 parts per billion (ppb) or higher was used to diagnose cough-variant asthma[6]; however, other studies reported lower values with NIOX-MINO® than with stationary models.[7] Cutoff values for diagnosis of disease have not been established. Matsunaga et al. reported that a FENO cutoff value of 24 ppb discriminated asthma from non-asthma with a sensitivity of 84.6% and a specificity of 92.6%. We defined normal as a FENO value of 23 ppb or less.[8, 9]

Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC ratio, peak expiratory flow (PEF), forced expiratory volume at 50% ($\dot{V}50$), and forced expiratory volume at 25% ($\dot{V}25$) were simultaneously measured using the Spirosift SP-310 desktop spirometer

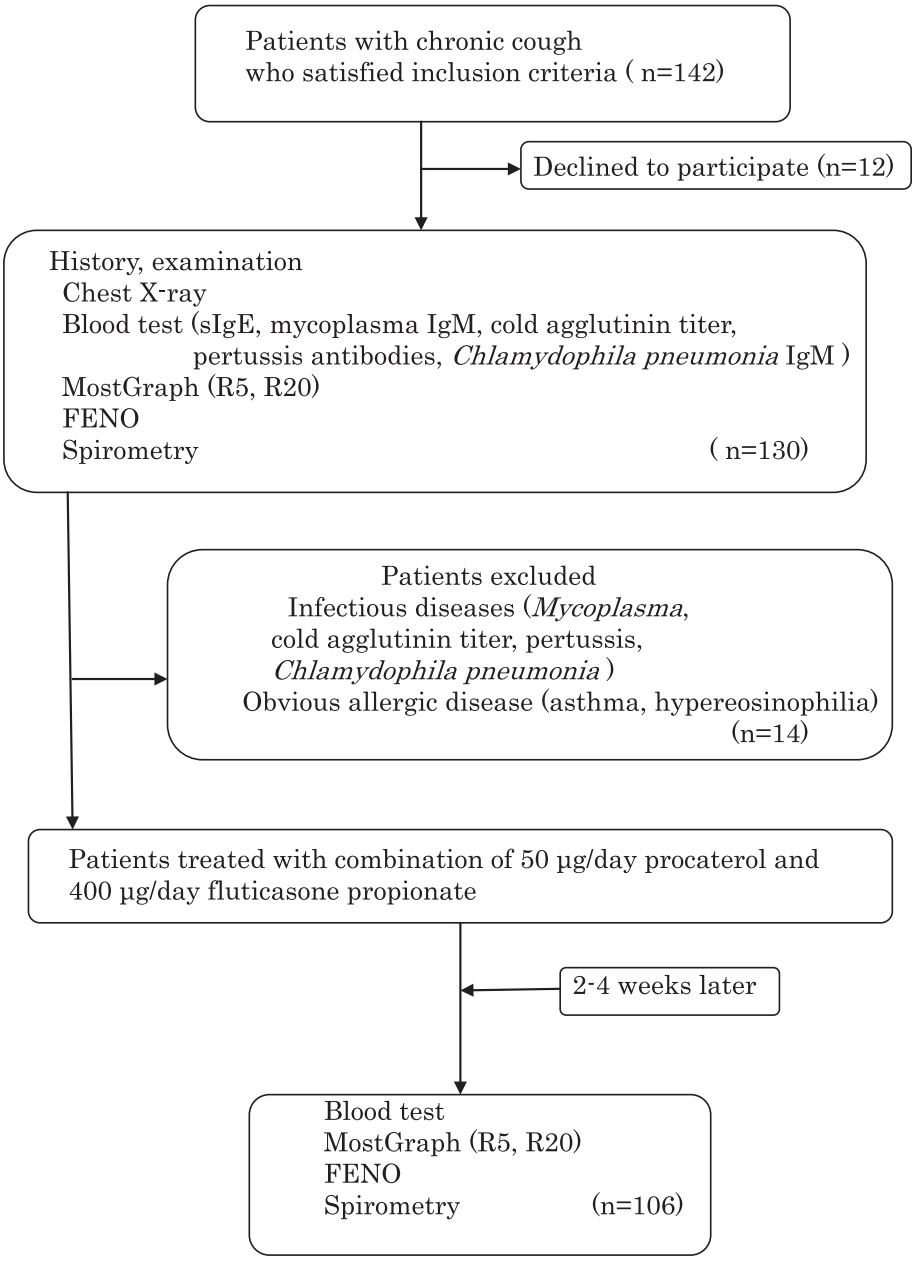


Fig. 1 Flow diagram of the progress of participants through the study.
sIgE: serum immunoglobulin E, IgM: immunoglobulin M, R5: resistance at 5 Hz, R20: resistance at 20 Hz, FENO: fractional exhaled nitric oxide

(Fukuda Denshi Co., Ltd., Tokyo, Japan).

The patients were treated with a combination of 50 µg/day of procaterol and 400 µg/day of fluticasone propionate. After 2 to 4 weeks the patients again underwent blood testing, MostGraph assessment, FENO measurement, and pulmonary function testing. In addition, the effectiveness of the prescribed drugs in relieving clinical symptoms was evaluated by using a visual analog scale (VAS). For assessment of cough, patients were asked to indicate the severity of their cough on a 10-cm linear scale on which 0 mm represented no cough and 100 mm the worst cough ever.

Global quality of life (QOL) was measured with a VAS, *i.e.*, a 10-cm horizontal line ranging from 0 (worst imaginable QOL) to 10 (perfect QOL).[10–12] In addition, patients were classified on the basis of their FENO values (FENO ≥24 vs ≤23 ppb) for the presence of eosinophilic inflammation.

Statistical analysis

A p value of less than 0.05 on the Wilcoxon signed-rank test was considered statistically significant. Correlations

Table 1 Baseline characteristics of patients with chronic cough and asthma

	Chronic cough	Asthma
Number of patients	106	32
Age (years)	44 ± 16	52 ± 13
Male/female	34/72	12/20
Smoking history (never/former)	76/30	76/32
Serum IgE (IU/ml)	145 ± 200	535 ± 623
Blood eosinophils (%)	3.04 ± 2.82	4.02 ± 3.74
VAS	5.96 ± 1.34	

Data are presented as mean ± SD, unless otherwise indicated
NO: nitric oxide, IgE: immunoglobulin E, VAS: visual analog score, SD: standard deviation

Table 2 Baseline clinical characteristics in the 2 treatment subgroups

	FENO (ppb)	
	FENO≥24	FENO≤23
Number of patients	51	55
Age (years)	42 ± 15	45 ± 16
Male/female	22/29	16/39
Smoking history (never/former)	11/40	36/19
Serum IgE (IU/ml)	183 ± 238	108 ± 146
Blood eosinophils (%)	3.90 ± 3.53	2.20 ± 1.45
VAS	6.41 ± 1.22	5.56 ± 1.32

Data are presented as mean ± SD, unless otherwise indicated.
FENO: fractional exhaled nitric oxide, IgE: immunoglobulin E, VAS: visual analog score, SD: standard deviation

Table 3 MostGraph measurements, exhaled nitric oxide level, and spirometry data before and after treatment

	Before	After
R5 (kPa/l/s)	3.13 ± 1.39	2.72 ± 1.22 *
R20 (kPa/l/s)	2.65 ± 0.95	2.34 ± 0.92 *
FENO (ppb)	30.32 ± 23.06	22.97 ± 17.50 *
FEV_1 (l/min)	2.65 ± 0.85	2.65 ± 0.88
PEF (l/min)	5.18 ± 2.42	5.37 ± 2.48
$\dot{V}50$ (l/min)	3.35 ± 1.41	3.50 ± 1.47
$\dot{V}25$ (l/min)	1.49 ± 0.82	1.65 ± 0.93
VAS	5.96 ± 1.34	3.62 ± 1.90 *

Results from 106 patients. Data are presented as mean score or mean ± SD. *$p < 0.05$
R5: resistance at 5 Hz, R20: resistance at 20 Hz, FENO: fractional exhaled nitric oxide, FEV_1: forced expiratory volume in 1 second, PEF: peak expiratory flow, $\dot{V}50$: forced expiratory volume at 50%, $\dot{V}25$: forced expiratory volume at 25%, VAS: visual analog score, SD: standard deviation

were assessed using the Spearman rank correlation coefficient.

Results

The baseline characteristics of the patients are shown in Tables 1 and 2. The VAS showed improvement in 92 of the 106 patients (86.8%), no change in 7 (6.6%), and worsening in 7 patients (6.6%), 3 of whom had poor treatment compliance.

MostGraph

There was a significant overall reduction in R5 and R20 during the course of treatment (Table 3, 4; Fig. 2〜4). There was no significant difference between the 2 groups (Table 4). Among the 10 patients whose VAS scores worsened, R5 increased in 6, R20 increased in 6, R5 decreased in 4, and R20 decreased in 4. Among 5 patients both R5 and R20 increased, while R5 and R20 both decreased among 3 patients. Among patients who experienced worsened

Table 4 MostGraph measurements and exhaled nitric oxide level before and after treatment in the 2 treatment subgroups

	FENO≥24		FENO≤23	
	Before	After	Before	After
R5 (kPa/l/s)	3.23 ± 1.27	2.90 ± 1.22 *	3.03 ± 1.49	2.56 ± 1.19 *
R20 (kPa/l/s)	2.76 ± 0.90	2.34 ± 0.89 *	2.66 ± 0.92	2.35 ± 0.93 *
FENO (ppb)	46.56 ± 25.60	29.14 ± 21.72 *	16.15 ± 1.27	16.92 ± 1.27

Results from 106 patients. FENO≥24 (n = 51), FENO≤23 (n = 55). Data are presented as mean score or mean ± SD. *p < 0.05
FENO: fractional exhaled nitric oxide, R5: resistance at 5 Hz, R20: resistance at 20 Hz, SD: standard deviation

symptoms, mean R5 was 1.57 $cmH_2O/l/s$ and mean R20 was 1.61 $cmH_2O/l/s$ before treatment. After treatment, the respective values were 1.99 $cmH_2O/l/s$ and 1.79 $cmH_2O/l/s$. R5 and R20 values. The values tended to decrease during treatment, but the change was not statistically significant. R5—R20 was difficult to evaluate because some values were negative.

Among patients with asthma, mean R5 was 2.77 $H_2O/l/s$ and mean R20 was 2.33 $H_2O/l/s$ (Table 5). There was no significant difference between patients with chronic cough and those with asthma.

FENO

Mean FENO significantly decreased during treatment, from 30.32 ppb before treatment to 22.97 ppb after treatment (Table 3). Mean FENO significantly decreased among patients with a pretreatment FENO of 24 ppb or higher but not among those with a FENO of 23 ppb or lower (Table 4; Fig. 5, 6).

Among patients whose VAS scores worsened, FENO increased in 7, remained unchanged in 2, and decreased in 1. Mean FENO in patients who experienced worsened symptoms was 13.9 ppb before treatment and 15 ppb after treatment.

Among patients with asthma, mean FENO was 42.57 ppb (Table 5). There was no significant difference between patients with chronic cough (FENO ≥24) and those with stable asthma.

Spirometry

$\dot{V}50$ decreased in 16 patients, and $\dot{V}25$ decreased in 28 patient; all other patients had normal lung function. FEV_1, FVC, FEV_1/FVC ratio, $\dot{V}50$, and $\dot{V}25$ did not significantly change during treatment (Table 3).

Among patients with asthma, mean $\dot{V}50$ was 2.33 and mean $\dot{V}25$ was 0.73 (Table 5).

There was no significant difference in FEV_1, FVC, $\dot{V}50$, or $\dot{V}25$.

In total, 84 patients underwent induced sputum testing; however, sputum was successfully collected from only 48 patients (approximately 57%) because many patients had a dry cough. The diagnostic utility of sputum testing was low.

There was no correlation between MostGraph and FENO variables during the course of treatment. In addition, there was no correlation between these variables among patients with a FENO of 24 ppb or higher or those with a FENO of 23 ppb or lower (Fig. 5, 6).

Discussion

In the past, invasive examinations such as the cough sensitivity test were necessary to determine the cause of chronic cough. However, MostGraph and FENO measurement can be performed easily on an outpatient basis, and reproducibility is excellent.[3, 13, 14]

In this study, although baseline R5 and R20 tended to be elevated in the participants, we observed a significant reduction in R5 and R20 during treatment. The decrease from baseline airway resistance was greater than 10%, both in participants with a FENO of 24 ppb or higher and those with a FENO of 23 ppb or lower. However, although FENO significantly decreased among participants with a high FENO, the change was not significant among those with a low pretreatment FENO. As mentioned above, these results suggest that increased airway resistance was involved in the development of chronic cough; thus, treatments that decreased airway resistance were effective.

A common cause of chronic cough is CVA,[15] which presents as airway hyperresponsiveness.[16] Pathologically, CVA has features in common with classical asthma, including eosinophilic inflammation and remodeling changes such as subbasement membrane thickening and goblet-

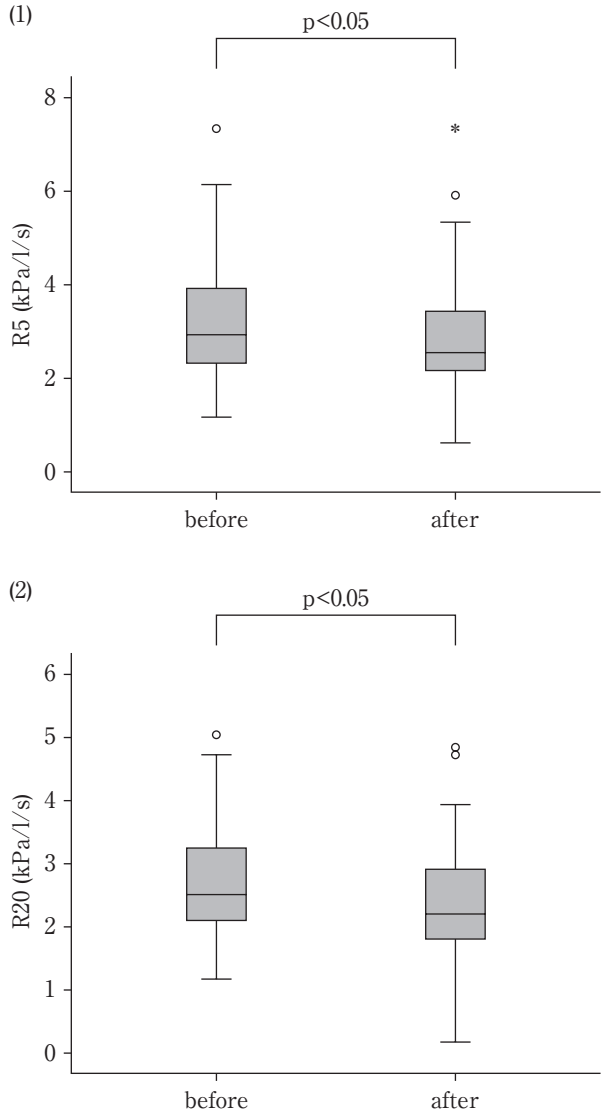


Fig. 2　(1) R5 before and after treatment (FENO≥24).
There was a significant overall reduction in R5 during the course of treatment.
(2) R20 before and after treatment (FENO≥24).
There was a significant overall reduction in R20 during the course of treatment.
R5: resistance at 5 Hz, R20: resistance at 20 Hz, FENO: fractional exhaled nitric oxide

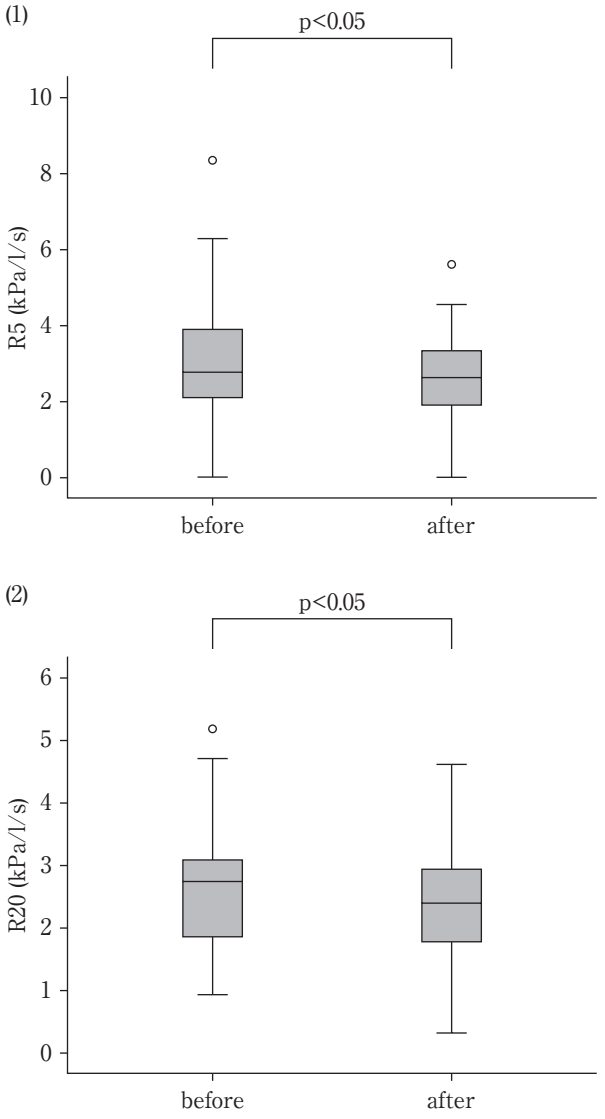


Fig. 3　R5 before and after treatment (FENO≤23).
(1) There was a significant overall reduction in R5 during the course of treatment.
(2) There was a significant overall reduction in R20 during the course of treatment.
R5: resistance at 5 Hz, R20: resistance at 20 Hz, FENO: fractional exhaled nitric oxide

cell hyperplasia.[17–22] Spasm of the airways and inflammatory changes in the bronchial mucosa may also contribute to increased airway resistance.

Chronic cough due to other causes, such as NAEB, is also characterized by airway inflammation and remodeling.[23–26] People with asthma and NAEB have a similar degree of submucosal eosinophilia and thickening of the basement membrane and lamina retiularis.[19, 23, 24] Submucosal changes in CVA and NAEB may be associated with airway resistance.

FENO is a useful marker of airway inflammation. Nitric oxide (NO) detected in expiration is produced by airway epithelial cells and macrophages.[27–29] NO in expiration is therefore significantly correlated with airway hyperresponsiveness and sputum eosinophils.[30–33] FENO is elevated in CVA[34, 35]; however, although FENO is usually higher in NAEB, its role in diagnosing NAEB has not been formally evaluated.[23, 36, 37] FENO is useful in evaluating patients with chronic cough as it can aid in diagnosing

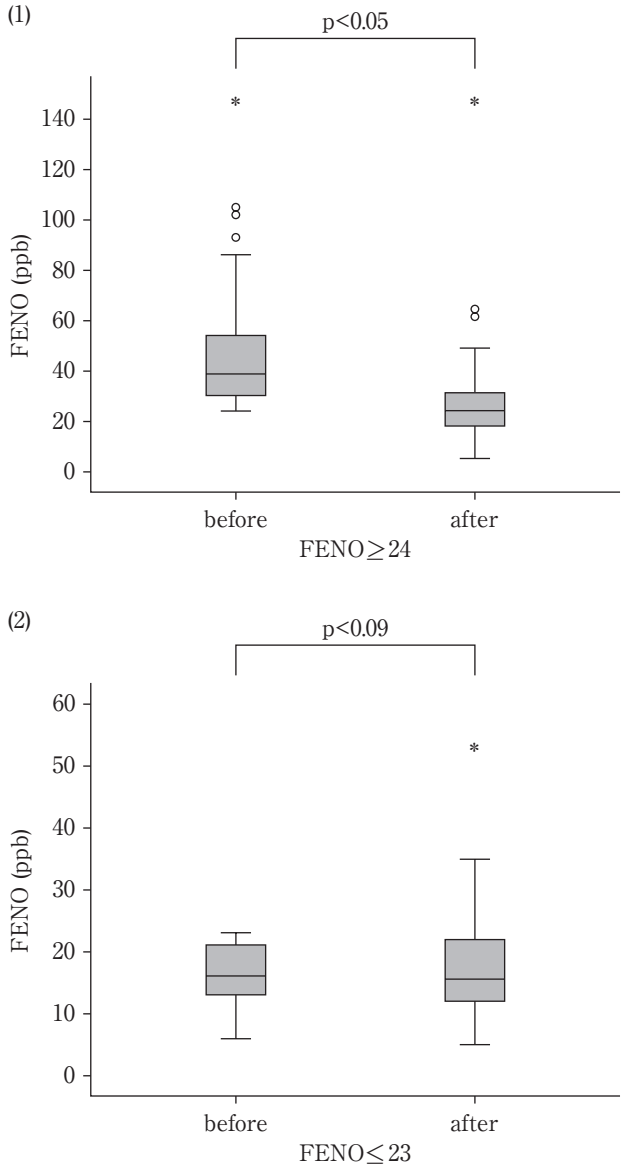


Fig. 4 FENO before and after treatment.
(1) There was a significant overall reduction in FENO during the course of treatment (FENO≥24).
(2) There was no significant overall reduction in FENO during the course of treatment (FENO≤23).
FENO: fractional exhaled nitric oxide

Table 5 MostGraph measurements, exhaled nitric oxide level, and spirometry data in asthma patients.

R5 (kPa/l/s)	2.77 ± 1.33
R20 (kPa/l/s)	2.33 ± 0.815
NO (ppb)	42.57 ± 38.80
FEV_1 (l/min)	3.25 ± 0.76
PEF (l/min)	6.78 ± 2.02
$\dot{V}50$ (l/min)	2.33 ± 1.70
$\dot{V}25$ (l/min)	0.73 ± 0.59

Results from 32 patients. Data are presented as mean score or mean ± SD. *p < 0.05
R5: resistance at 5 Hz, R20: resistance at 20 Hz, NO: nitric oxide, FEV_1: forced expiratory volume in second, PEF: peak expiratory flow, $\dot{V}50$: forced expiratory volume at 50%, $\dot{V}25$: forced expiratory volume at 25%

eosinophilic airway disease and predicting response to inhaled corticosteroids.[38] Our findings suggest that airway and eosinophilic inflammation are present in patients with high FENO levels.

There were no significant differences in FENO, pulmonary function, or airway resistance between patients with chronic cough (FENO ≥24) and those with stable asthma. These findings suggest that there are similar pathological conditions in stable asthma and chronic cough with eosinophilic inflammation.

FENO is used to predict response to inhaled corticosteroid therapy, which suggests that patients with chronic cough and a high FENO should be treated with inhaled corticosteroid.

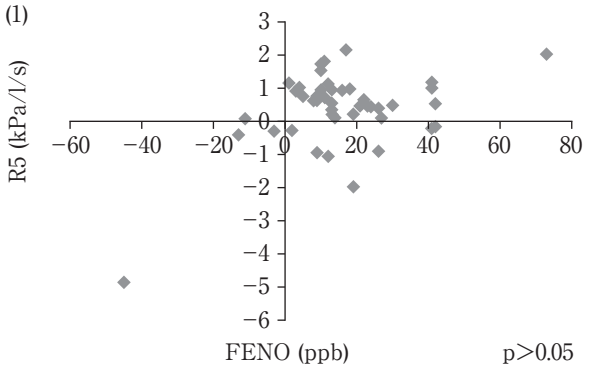
FENO measurement might be helpful in monitoring the effectiveness of anti-inflammatory treatment. Moreover, an elevated FENO might indicate uncontrolled eosinophilic inflammation.

FENO values were low among patients whose symptoms did not improve (excepting the 3 patients with poor compliance). These patients also tended to have low R5 and R20 values. Furthermore, because no significant changes were seen during treatment, it is possible that airway inflammation was not a factor in these patients. Because R5 and R20 tended not to increase in MostGraph analyses, it was necessary to consider causes other than those associated with the airway, such as allergic laryngitis and psychogenic cough.

There was no correlation between airway resistance and FENO; therefore, increased airway resistance does not always reflect the degree of eosinophilic inflammation. Frequency-dependence of airway resistance was not observed in either group.

Our findings suggest that a combination of MostGraph and FENO measurement is useful in evaluating different pathophysiological mechanisms, such as airway remodeling and eosinophilic inflammation, and in treating the underlying disease in patients with chronic cough.

CVA is highly likely in patients with increased airway resistance and elevated FENO, whereas the presence of



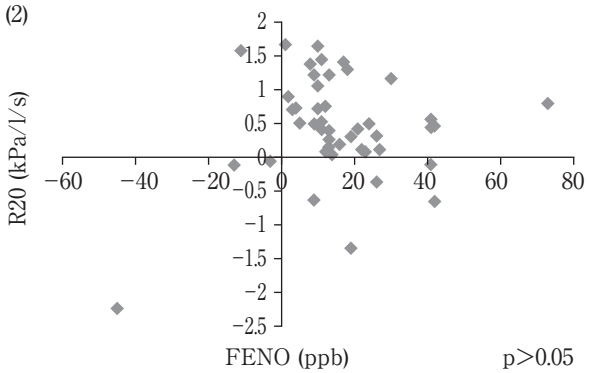
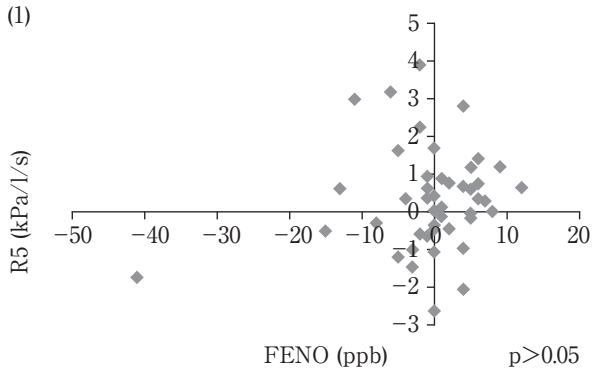


Fig. 5 (1) Correlation between exhaled nitric oxide level and MostGraph parameters (R5) before and after treatment (FENO≥24)
There was no correlation between MostGraph and FENO variables.
(2) Correlation between exhaled nitric oxide level and MostGraph parameters (R20) before and after treatment (FENO≥24).
There was no correlation between MostGraph and FENO variables.
R5: resistance at 5 Hz, R20: resistance at 20 Hz, FENO: fractional exhaled nitric oxide



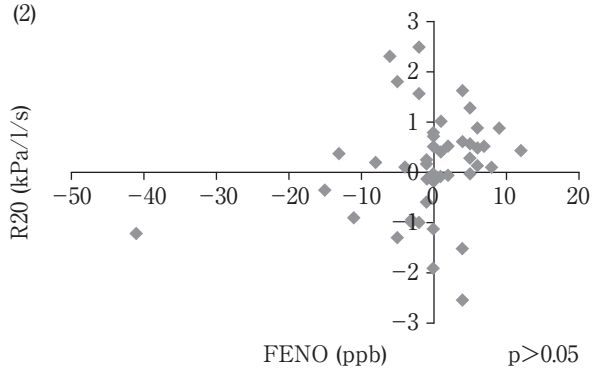


Fig. 6 (1) Correlation between exhaled nitric oxide level and MostGraph parameters (R5) before and after treatment (FENO≤23).
There was no correlation between MostGraph and FENO variables.
(2) Correlation between exhaled nitric oxide level and MostGraph parameters (R20) before and after treatment (FENO≤23).
There was no correlation between MostGraph and FENO variables.
R5: resistance at 5 Hz, R20: resistance at 20 Hz, FENO: fractional exhaled nitric oxide

increased airway resistance alone suggests CVA or NAEB. Inhaled corticosteroids and β stimulators are effective first-line therapies in such patients. In patients with normal airway resistance and FENO, conditions other than airway inflammation should be suspected.

The results of pulmonary function tests did not significantly change during treatment in the present study. In induced sputum testing,[39] sputum was collected from 48 patients (57%). However, due to the presence of dry cough, spontaneous sputum tests could not be performed in many participants. The diagnostic utility of tests of pulmonary function and sputum was low.

Our findings suggest that a decrease of greater than 10% in airway resistance results in substantial improvement. The presence of decreased airway resistance and FENO after treatment may aid in the diagnosis of chronic cough. However, the combination of MostGraph and FENO measurement was not sufficient for this task, and further tests may be needed to establish a definitive diagnosis. Nonetheless, concomitant monitoring of decreased airway resistance (with MostGraph) and improved eosinophilic inflammation (with FENO) was very effective for objective therapeutic evaluation.

The decision to stop treatment is usually based on resolution of subjective symptoms; however, by using a combination of MostGraph and FENO measurement, objective signs of normalized FENO and airway resistance might become the index. Furthermore, patients with persistent abnormalities in FENO and airway resistance require careful follow-up for other potential diseases and develop-

ment of bronchial asthma.

MostGraph and FENO are quick and noninvasive in all patients, including those who may have contraindications, and can yield useful information at the initial consultation.

Conclusion

R5 and R20 tended to be elevated in patients with chronic cough, but both decreased with treatment. There was no correlation between airway resistance and FENO; therefore, increased airway resistance does not always reflect the degree of eosinophilic inflammation. In addition, our findings suggest that there were similar pathological conditions between stable asthma and chronic cough with eosinophilic inflammation.

Combined MostGraph and FENO measurement is quick and noninvasive and provides vital information on the pathophysiology and management of chronic cough. Furthermore, these techniques appear to be useful in assessing treatment effectiveness.

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Conflicts of interest: None declared.

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慢性咳嗽におけるモストグラフ法と呼気 NO 測定意義についての検討

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要約

目的：慢性咳嗽患者を対象にモストグラフ法，fractional exhaled nitric oxide（FENO）測定，肺機能検査を行った．慢性咳嗽の鑑別診断，治療効果判定に対してモストグラフ法，FENO 測定，肺機能検査の測定意義および有効性について検討した．

方法：慢性咳嗽を主訴に来院した患者 106 名と安定期の気管支喘息患者 32 名を対象とした．気道抵抗測定は呼吸抵抗装置 MostGraph-01［チェスト（株），東京］を用いた．FENO は NIOX-MINO®（Aerocrine AB, Solma, Sweden）を用いた．肺機能検査はスパイロメトリー［フクダ電子（株），東京］を使用した．治療薬は β 刺激薬，吸入ステロイド薬の併用を中心とした．治療前後で結果を比較した．また同様の検査を行い慢性咳嗽患者と比較検討をした．

結果：5 Hz における気道抵抗（resistance at 5 Hz：R5），20 Hz における気道抵抗（resistance at 20 Hz：R20）は慢性咳嗽患者では高い傾向にあった．症状の改善とともに気道抵抗と FENO は有意な減少を認めた．肺機能検査では有意な変化は認めなかった．

気管支喘息患者との比較では，気道抵抗，肺機能検査は有意差を認めなかったが，気管支喘息患者において FENO の有意な上昇を認めた．

結論：慢性咳嗽患者では R5，R20 が高い傾向にあり，治療により低下した．気道抵抗と FENO は相関を認めず，慢性咳嗽の病態に気道抵抗の上昇が関与し，これは必ずしも好酸球炎症の程度を反映するものではないと考えられた．

気管支喘息患者と FENO≥24 群の慢性咳嗽患者では FENO, 気道抵抗と肺機能は有意差が認められなかった．好酸球炎症を伴う慢性咳嗽と安定期の気管支喘息は似通った病態であることが推測された．

モストグラフ法，FENO 測定は慢性咳嗽の鑑別診断には至らないが簡便性と迅速性から慢性咳嗽の治療方針の早期決定，治療効果判定に有用である可能性が示唆された．

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