

Original Article

Clinical Characteristics of Cough Frequency Patterns in Patients with and without Asthma

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What is already known about this topic? Cough is a frequent symptom of asthma. Cough frequency monitoring devices are now available to objectively measure cough counts. However, little is known about differences in cough frequency between patients with and without asthma.

What does this article add to our knowledge? Nocturnal cough in asthmatic patients was more frequent and improved greater after appropriate treatment than that in nonasthmatic patients. In addition, nocturnal cough in asthma can be associated with bronchial hyperresponsiveness.

How does this study impact current management guidelines? Nocturnal cough frequency in asthmatic patients is different from that in nonasthmatic patients and may provide unique and valuable information on making an early prediction of therapeutic effects in asthma.

BACKGROUND: Cough is a frequent symptom of asthma. Cough frequency (CoFr) monitoring devices are now available to objectively measure cough counts and offer a novel endpoint to assess asthma. However, little is known about CoFr in asthma. **OBJECTIVE:** The aims were, first, to determine whether unique features of CoFr exist in asthmatic and nonasthmatic patients and, secondly, to evaluate relationships between CoFr and pathophysiological parameters of asthma. **METHODS:** In the current study, 73 asthmatic and 63 nonasthmatic patients suffering from persistent cough were enrolled. At study entry, the Leicester Cough Questionnaire (LCQ health status), cough visual analog scale (VAS), Leicester

Cough Monitor (LCM), fractional exhaled nitric oxide (FeNO) measurements, and spirometry were performed. In asthmatic patients, the bronchial hyperresponsiveness (BHR) test was conducted if applicable. In 28 asthmatic and 17 nonasthmatic patients, LCQ, VAS, and LCM were examined before and after treatment.

RESULTS: CoFr during nighttime (asleep) was significantly higher in asthmatic patients than in nonasthmatic patients. Twenty-four-hour CoFr significantly decreased after appropriate treatment and was correlated with changes in VAS and LCQ in all patients. The improvement in cough in asthmatic patients was greater during nighttime than during daytime (awake). CoFr in asthmatic patients was significantly correlated with BHR, but not with FeNO.

CONCLUSIONS: In asthmatic patients, nocturnal CoFr can be associated with BHR, was significantly higher before treatment, but improved more after treatment compared with nonasthmatic patients. Monitoring nocturnal CoFr may provide unique and valuable information on making an early prediction of therapeutic effects in asthma. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: Asthma; Persistent cough; Leicester Cough Monitor; Nocturnal cough; Bronchial hyperresponsiveness

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Cough, wheeze, chest tightness, and dyspnoea are regarded as the major symptoms of asthma. Cough, especially nocturnal cough, is the most common complaint among these classical symptoms.¹⁻³ According to epidemiological cough surveys in Japan, asthma or cough variant asthma account for 25% to 70%

Abbreviations used

ACT- Asthma Control Test

c/h- Coughs per hour

CoFr- Cough frequency

Dmin- Minimum dose of methacholine

FeNO- Fractional exhaled nitric oxide

FEV₁- Forced expiratory volume in 1 second

IQR- Interquartile range

LCM- Leicester Cough Monitor

LCQ- Leicester Cough Questionnaire

SD- Standard deviation

VAS- Visual analog scale

of patients who are suffering from persistent cough.⁴⁻⁶ In addition, cough also predicts the severity,^{3,7,8} control status,⁹ and prognosis¹⁰ of asthma. Furthermore, unlike wheezing, dyspnoea, and chest tightness, cough can be evaluated by not only subjective measures, such as the visual analog scale (VAS) and Leicester Cough Questionnaire (LCQ),^{11,12} but also quantified objectively using an ambulatory monitoring system.^{12,13} Thus, monitoring cough may provide useful information on understanding the pathophysiology of asthma and also has a strong impact on improving the health status of asthmatic patients.

The utility of ambulatory cough monitoring systems has previously been reported in patients with asthma,^{9,14-16} as well as acute cough,¹⁷ chronic obstructive pulmonary disease,¹⁸ sarcoidosis,¹⁹ and bronchiectasis.²⁰ All studies demonstrated that cough frequency (CoFr) was greater compared with healthy subjects.^{9,14-20} Especially in asthma studies, CoFr correlated well with poor asthma control status, worsening asthma symptoms, and an impaired quality of life.^{9,15,16} Thus, CoFr monitoring can be used as a novel endpoint to assess cough status in asthma. However, there were no correlations between CoFr and objective parameters such as airway inflammation, airflow obstruction, and bronchial hyperresponsiveness.^{9,15} It remains uncertain as to why CoFr was not pathophysiologically related to asthma. In addition, little investigation has been made into whether CoFr patterns differ between asthmatic patients and patients with other respiratory disorders. Furthermore, to our knowledge, there have been no reports that evaluate CoFr improvement after appropriate treatment in patients with and without asthma.

Therefore, the aims of the current study were, first, to determine whether unique features of CoFr exist in asthmatic and nonasthmatic patients and, secondly, to evaluate relationships between CoFr and the parameters such as airway inflammation, airflow obstruction, and bronchial hyperresponsiveness in asthma.

METHODS

Patients

In total, 73 asthmatic patients and 63 nonasthmatic patients, both of whom complained of persistent cough for more than 3 weeks, were recruited from the Department of Pulmonary Medicine at Fukushima Medical University Hospital. Forty-four of the 73 asthmatic patients were newly diagnosed as having asthma at enrolment, and the remaining 29 were uncontrolled or partially controlled asthmatic patients who had already been treated in line with the Japanese guidelines for adult asthma.²¹ The diagnosis of asthma was made by respiratory physicians according to the clinical

history of characteristic symptoms (ie, recurrent coughing, wheezing, chest tightness, and breathlessness), as well as either forced expiratory volume in 1 second (FEV₁) reversibility $\geq 12\%$, positive bronchial hyperresponsiveness to methacholine (minimum dose of methacholine [Dmin] < 12.5 units using the Astograph method),²² or sputum eosinophilia of $\geq 3\%$. Patients with any respiratory disease other than asthma were classified as nonasthmatic patients. Their diagnosis was made based on the Japanese Respiratory Society guidelines for management of cough while performing blood tests, chest X-rays, chest computerized tomography scan if required, spirometry, assessment of the response to disease-specific treatments, sputum culture, and sputum cytology.²³ This study was approved by the Ethics Committee of Fukushima Medical University and registered to UMIN (UMIN000010531). All participants provided written informed consent.

Cough frequency monitoring

Subjects underwent ambulatory cough sound recording using a portable MP3 sound recorder with a free-field microphone (PR-XS455; Panasonic Corporation, Osaka, Japan), worn for 24 hours in the patient's own environment. Then, objective 24-hour CoFr was detected using the Leicester Cough Monitor (LCM) software, a validated ambulatory cough monitoring system.^{12,13} In brief, the sound files were uploaded onto a computer for automated analysis using a specifically designed cough detection software described previously.^{13,17,19,20} Objective CoFr was determined by counting all cough events individually, whether occurring in isolation or within coughing bouts. Patients were also asked to record when they went to sleep and when they woke up in a diary. The number of cough sounds was expressed as coughs per hour (c/h).

Cough-specific questionnaires

The LCQ was used to assess the impact of cough on the patients' health-related quality of life. The cough-specific VAS (0-100 mm) was used to assess cough severity.¹² The LCQ is a well-validated cough-specific health status questionnaire for adults with cough.^{11,12} This questionnaire comprises 19 cough-specific questions divided into 3 domains (physical, psychological, and social) and uses a 7-point Likert response scale. Scores for each domain range from 1 to 7 and the overall score ranges from 3 to 21, with a higher score indicating a better quality of life.

Spirometry and fractional exhaled nitric oxide (FeNO) measurements

FeNO measurements (NA623N; Chest M.I., Inc., Tokyo, Japan) followed by spirometry (Chestac-8900; Chest M.I., Inc.) were performed in line with international guidelines.^{24,25}

Bronchial hyperresponsiveness test

A test for bronchial hyperresponsiveness to methacholine was performed using the Astograph method (Jupiter 21; Chest M.I., Inc.).²⁶ Patients inhaled methacholine diluted in physiologic saline (starting with physiologic saline only as a control) at gradually increasing concentrations of 49, 98, 195, 390, 781, 1563, 3125, 6250, and 12,500 mg/mL, and airway resistance was continuously measured. A dose-response curve was drawn for methacholine and airway pressure, and Dmin was calculated as an index of bronchial responsiveness. Positive bronchial hyperresponsiveness was defined as a value of < 12.5 units.²²

TABLE I. The diagnoses of patients with persistent cough

Diagnosis	N = 136	Percentage
Bronchial asthma	73	53.7
Post nasal drip	12	8.8
Nonasthmatic eosinophilic bronchitis	10	7.4
COPD	10	7.4
Chronic unexplained cough	8	5.9
Postacute pneumonia, acute bronchitis	4	2.9
Interstitial pneumonia	3	2.2
Postinfectious cough	2	1.5
Allergic bronchopulmonary aspergillosis	2	1.5
Lung cancer	2	1.5
Chronic bronchiolitis	2	1.5
Mycobacterium tuberculosis	2	1.5
Nontuberculosis mycobacteria	1	0.7
Whooping cough	1	0.7
Eosinophilic pneumonia	1	0.7
Eosinophilic bronchiolitis	1	0.7
Gastroesophageal reflux disease	1	0.7
Drug-induced cough	1	0.7

COPD, Chronic obstructive pulmonary disease.

Study design

This was a cross-sectional observational study. At study entry, LCQ and VAS were administered, and then FeNO measurements, spirometry, and LCM were performed on all patients. In newly diagnosed asthmatic patients, either a reversibility test to bronchodilator or a bronchial hyperresponsiveness test was conducted for a definite diagnosis of asthma. In uncontrolled or partially controlled asthmatic patients, despite appropriate treatments, an Asthma Control Test (ACT) questionnaire was additionally administered.²⁷ In 28 asthmatic patients and 17 nonasthmatic patients, LCQ, VAS, and LCM were performed before and after treatment. All asthmatic patients were treated with inhaled corticosteroids either alone or with long-acting β_2 -agonists. For nonasthmatic patients, once a definite diagnosis was made, they received a standard treatment specific to each disorder without using antitussive drugs, based on the Japanese Respiratory Society guidelines for management of cough.²³ If a diagnosis of chronic unexplained cough was made, patients were treated with central antitussives such as codeine phosphate and eprazinone hydrochloride either alone or with tricyclic antidepressants.

Statistical analysis

Statistical analyses were performed using SPSS for Windows (version 21.0; IBM, Armonk, NY) and GraphPad Prism (version 5.0 for Windows; GraphPad Software, San Diego, Calif). According to the power calculation, a sample size of 64 patients in each group of asthmatic or nonasthmatic patients would provide approximately 80% power to detect a 20% difference in 24-hour CoFr. The distributions of data were assessed using the Shapiro-Wilk test. Parametric data were expressed as mean with standard deviation (SD), whereas nonparametric data were expressed as median with interquartile range (IQR). CoFr was logarithmically transformed and presented as geometric mean with SD. Parametrically distributed data were analyzed with independent sample *t*-tests to compare sample means, whereas the comparison of nonparametric data was carried out using the Mann-Whitney *U* test. Correlations of continuous variables were evaluated using Spearman's rank

correlation coefficient analysis. A 2-tailed *P* value of less than .05 was considered statistically significant.

RESULTS

Characteristics of patients

In total, definite diagnoses were made in 136 patients with persistent cough (Table I). Of these, asthmatic patients accounted for 53.7%. We then divided the patients into 2 groups: patients with and without asthma (Table II). The asthmatic patients were significantly younger and had a higher proportion of females than the nonasthmatic patients. There were no significant differences in lung function parameters, as well as in the cough-specific questionnaires, between the asthmatic and nonasthmatic patients.

Difference in CoFr between asthmatic and nonasthmatic patients.

There was no significant difference in 24-hour CoFr between the asthmatic and nonasthmatic patients (median [IQR]: 12.0 [5.0, 29.5] vs 8.0 [4.0, 22.0] c/h, *P* = .08) (Figure 1, A). Similarly, no significant difference in CoFr during daytime (awake) was observed between the patients (median [IQR]: 15.6 [6.9, 34.8] vs 10.8 [5.9, 26.8] c/h, *P* = .2) (Figure 1, B). On the other hand, CoFr during nighttime (asleep) in the asthmatic patients was significantly higher than that in the nonasthmatic patients (median [IQR]: 4.7 [1.7, 13.7] vs 1.75 [0.5, 4.3] c/h, *P* < .001) (Figure 1, C). The ratio of CoFr during nighttime (asleep) to that during daytime (awake) was also significantly higher in the asthmatic patients compared with the nonasthmatic patients (median [IQR]: 0.3 [0.2, 0.6] vs 0.2 [0.05, 0.5], *P* = .009) (Figure 1, D). The differences in CoFr obtained above were not influenced by the presence or absence of treatment for cough (data not shown). The CoFr in females was significantly higher than that in males regardless of having asthma or not (*P* < .05).

CoFr before and after treatment. As expected, 24-hour CoFr after appropriate treatment was significantly lower than that before treatment in all patients (median [IQR]: 2.0 [1.0, 6.5] vs 18.0 [8.0, 36.0] c/h, *P* < .001; Figure 2, A). This significant reduction in 24-hour CoFr after treatment was consistently observed both in the asthmatic patients (median [IQR]: 3.5 [1.0, 5.8] vs 21.0 [11.3, 34.8] c/h, *P* < .001; Figure 2, B) and the nonasthmatic patients (median [IQR]: 1.0 [1.0, 8.0] vs 12.0 [6.5, 41.0] c/h, *P* < .001; Figure 2, C).

Correlations of changes in cough parameters before and after treatment.

When changes in CoFr, LCQ, and VAS before and after treatment expressed as Δ CoFr, Δ LCQ, and Δ VAS, respectively, were compared, Δ CoFr was significantly correlated with not only Δ LCQ but also Δ VAS (r_s = 0.52 and -0.57, respectively; *P* < .001). These significant correlations between Δ CoFr, Δ LCQ, and Δ VAS could be observed in the asthmatic patients (r_s = 0.60, *P* = .001 and r_s = -0.78, *P* < .001, respectively), but not in the nonasthmatic patients (r_s = 0.33, *P* = .21 and r_s = -0.31, *P* = .25, respectively).

Correlations of CoFr improvement rate before and after treatment. There were significant positive correlations of 24-hour Δ CoFr with daytime as well as nighttime Δ CoFr in both the asthmatic (r_s = 0.97, *P* < .001; Figure 3, A, and

TABLE II. Characteristics of patients

	Total (n = 136)	Asthmatic patients (n = 73)	Nonasthmatic patients (n = 63)	P value
Age, y*	60.0 (45.3, 72.8)	54.0 (43.0, 67.5)	67.0 (48.0, 75.0)	.02
Gender (M/F)	51/85	21/52	30/33	.02
Height	158.1 (8.1)	158.3 (8.1)	158.0 (8.3)	.7
Weight*	59.9 (53.5, 67.0)	61.1 (53.8, 68.0)	58.2 (52.0, 65.4)	.1
Smoking status (current/former/never)	11/36/89	5/18/50	6/18/39	.6
Cough duration, mo*	6.0 (2.0, 45.0)	6.0 (2.0, 42.0)	6.0 (2.0, 60.0)	.6
FEV ₁ , L	2.18 (0.67)	2.17 (0.59)	2.19 (0.76)	.8
%FEV ₁ , %	90.2 (21.7)	89.5 (20.5)	91.0 (23.2)	.7
FVC, L	2.93 (0.79)	2.89 (0.73)	2.97 (0.87)	.5
%FVC, %	98.6 (18.1)	98.1 (18.0)	99.3 (18.2)	.7
FeNO, ppb*	30.8 (17.7, 65.1)	38.0 (17.1, 84.8)	26.9 (17.8, 39.1)	.05
ACT, pts (n = 36)	15.9 (4.6)	15.9 (4.6)	NA	NA
Dmin, Unit* (n = 52)	2.3 (0.3, 20.3)	1.1 (0.2, 4.2)	19.8 (0.7, 44.5)	.004
LCQ total, pts*	12.8 (9.7, 15.3)	12.6 (8.9, 15.3)	12.9 (10.4, 15.5)	.3
LCQ physical, pts	4.5 (1.2)	4.2 (1.1)	4.5 (1.2)	.1
LCQ psychological, pts	4.1 (1.2)	4.0 (1.1)	4.1 (1.4)	.5
LCQ social, pts*	4.3 (3.0, 5.3)	4.0 (2.8, 5.3)	4.3 (3.3, 5.5)	.4
VAS severity, mm*	53.0 (32.0, 70.0)	60.0 (35.0, 73.0)	50.0 (30.0, 66.8)	.08
VAS frequency, mm*	51.0 (32.0, 77.0)	54.0 (34.0, 82.0)	48.0 (27.0, 68.5)	.1

Data are presented as mean (standard deviation), n, or medians (interquartile range) when appropriate.

ACT, Asthma Control Test; Dmin, minimum dose of methacholine; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; LCQ, Leicester Cough Questionnaire; NA, not applicable; VAS, visual analog scale.

*Data are presented as medians (IQR).

$r_s = 0.69$, $P < .001$; Figure 3, B, respectively) and nonasthmatic patients ($r_s = 0.94$, $P < .002$; Figure 3, C, and $r_s = 0.54$, $P = .03$; Figure 3, D, respectively). Δ CoFr during nighttime was likely to be diverse compared with that during daytime regardless of having asthma or not.

Time course of CoFr improvement after appropriate treatment for cough. Similar to previous reports, absolute reductions in CoFr ($\text{CoFr}_{[\text{before treatment}]} - \text{CoFr}_{[\text{after treatment}]}$) after treatment were significantly greater during daytime than during nighttime in both the asthmatic patients (median [IQR]: 21.9 [7.1, 37.0] vs 6.3 [3.5, 18.0] c/h, $P = .001$) (Figure 4, A) and nonasthmatic patients (median [IQR]: 13.2 [4.0, 34.8] vs 2.2 [0.8, 9.4] c/h, $P = .004$) (Figure 4, B). In addition, an improvement rate of CoFr after treatment was calculated by " $(\text{CoFr}_{[\text{before treatment}]} - \text{CoFr}_{[\text{after treatment}]})/\text{CoFr}_{[\text{before treatment}]} \times 100$ " to investigate differences in prognosis between the patients with and without asthma. Interestingly, in the asthmatic patients, the improvement rate of CoFr during nighttime was significantly greater than that during daytime (median [IQR]: 94.9 [70.4, 100] % vs 83.5 [53.6, 92.7] %, $P = .01$) (Figure 4, C). On the contrary, this change was not observed in the nonasthmatic patients (median [IQR]: 79.4 [38.9, 99.6] % vs 76.7 [46.2, 94.6] %, $P = .9$) (Figure 4, D).

Correlations between CoFr and parameters related to asthma pathophysiology. In the asthmatic patients, CoFr showed no correlations with FeNO ($r_s = -0.06$, $P = .5$) and %predicted FEV₁ ($r_s = -0.10$, $P = .4$). On the other hand, CoFr had weak but significant correlations with Dmin ($r_s = -0.38$, $P = .04$) and ACT score ($r_s = -0.43$, $P = .01$).

DISCUSSION

To our knowledge, this is the first study to evaluate the difference in CoFr patterns between patients with and without asthma and to also investigate how coughing improves after appropriate treatment for cough. The current study found that objective CoFr during nighttime was greater in the asthmatic patients than in nonasthmatic patients, although there were no significant differences in daytime CoFr between the 2 groups. In addition, a significant reduction in 24-hour CoFr was observed in all patients after appropriate treatment. Interestingly, CoFr during nighttime improved particularly greater than that during daytime in the asthmatic patients when compared with the nonasthmatic patients. Finally, CoFr in asthma was associated with bronchial hyperresponsiveness, but not with allergic airway inflammation indicated by FeNO.

As expected, a significant improvement of 24-hour CoFr after appropriate treatment was observed in the current study. Until now, subjective measures, such as VAS and LCQ, were often used for assessing therapeutic effects on persistent cough.^{12,28,29} However, they are not disease specific and their assessments are susceptible to the patients' perception of their symptoms.¹² Recently, CoFr monitoring devices for objectively measuring coughs have been frequently used to assess the effects of new antitussive drugs on chronic cough in clinical trials.³⁰⁻³² However, there have been only a few studies that have evaluated disease management using a CoFr monitoring system in routine clinical practice. Van Manen et al³³ conducted a study to evaluate the efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis with cough and revealed that pirfenidone treatment significantly reduced 24-hour cough counts by 34% and improved cough status evaluated by VAS and LCQ. Marsden et al⁹ found that increased cough rates were associated with worsening asthma control status and suggested that the

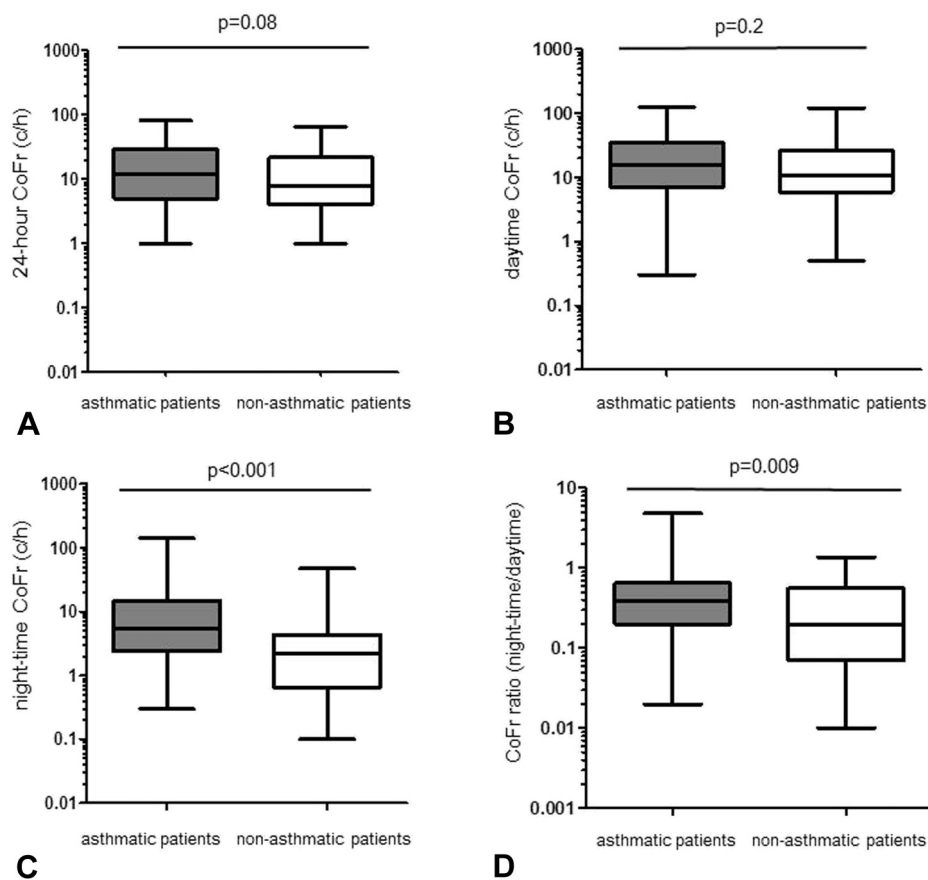


FIGURE 1. Comparisons of cough frequency (CoFr) over 24 hours (A), during daytime (B), and during nighttime (C) between patients with and without asthma. A comparison of the CoFr ratio during nighttime (asleep) with that during daytime (awake) between patients with and without asthma (D). The thick bar is the median value and the shaded box represents the interquartile range.

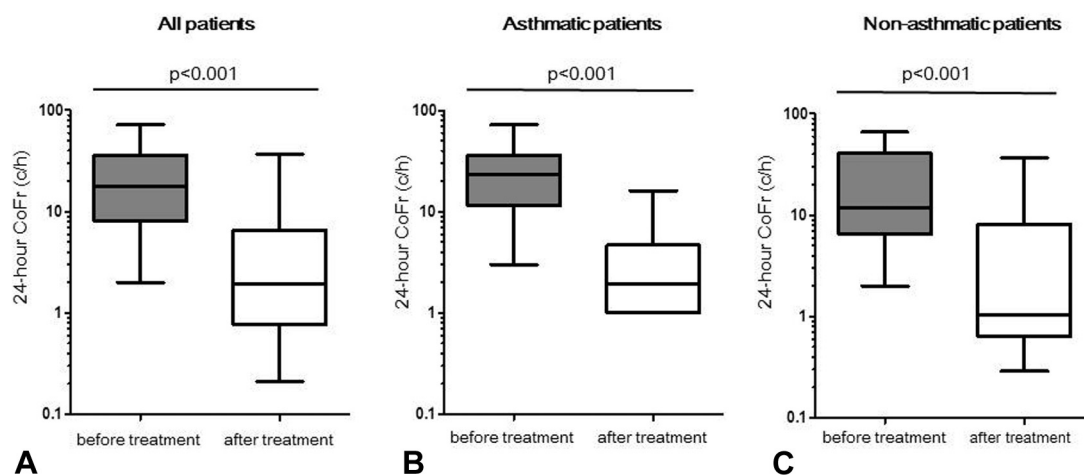


FIGURE 2. Comparisons of cough frequency (CoFr) before and after treatment in all patients (A), in the asthmatic patients (B), and in the nonasthmatic patients (C). The thick bar is the median value and the shaded box represents the interquartile range.

rates may provide unique information on asthma control, which is not fully captured by spirometry or the asthma control questionnaire. These findings indicate that CoFr monitoring can be used as an additional assessment tool for cough management in respiratory disorders.

More interestingly, the current study demonstrated that the improvement rate of CoFr during nighttime was greater than that during daytime only in the asthmatic patients (Figure 4, C) although absolute reductions in CoFr were significantly greater during daytime than nighttime in both asthmatic and

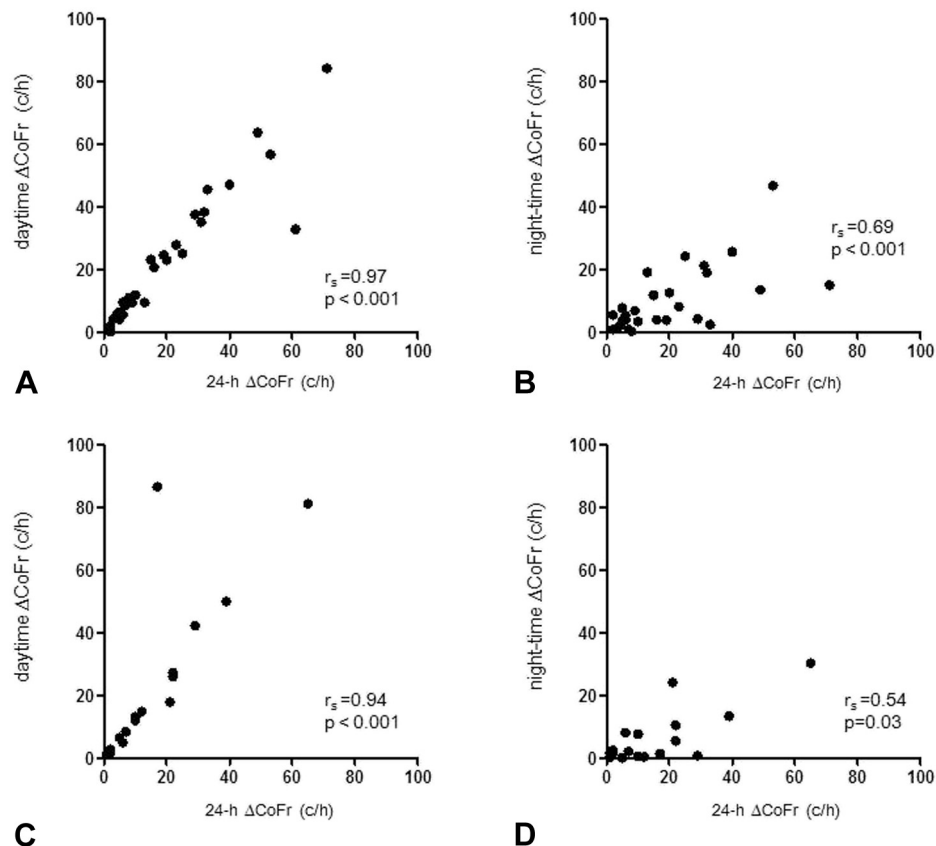


FIGURE 3. Correlations between changes in cough frequency (ΔCoFr) in a day and daytime ΔCoFr (A), and nighttime ΔCoFr (B) in the asthmatic patients, and correlations between changes in cough frequency (ΔCoFr) in a day and daytime ΔCoFr (C), and nighttime ΔCoFr (D) in the nonasthmatic patients.

nonasthmatic patients (Figure 4, A and B). At present, to our knowledge, there have been no studies evaluating the time course of cough improvement after treatment for cough. Our study is the first to reveal that the time course of cough improvement clearly differs between patients with and without asthma. The possible reason for this difference in terms of therapeutic response can be explained by the distinct mechanisms between asthmatic cough and nonasthmatic cough. Generally, nonasthmatic patients cough more frequently during daytime than nighttime.^{13,33-35} This is because the cough reflex pathway, where peripheral nerve endings in the airways transverse through the vagal nerve to the brainstem cough center, is highly sensitive during the day but suppressed at night.³⁶ Thus, the central antitussives can be somewhat effective against cough in nonasthmatic patients. On the other hand, nocturnal cough predominant in asthmatic patients is accompanied by increased bronchial hyperresponsiveness and airway inflammation during nighttime.^{16,37-39} In addition, alterations in β_2 -adrenergic and glucocorticoid receptor function, as well as blunted hypothalamic-pituitary-adrenal axis function, might play an important role in modulating nocturnal cough.³⁷ Our result of the negative correlation between CoFr and bronchial hyperresponsiveness may possibly support the above-mentioned mechanisms. Thus, taking these reports, as well as our findings, into consideration, treatment with inhaled corticosteroid either alone or with a β_2 -agonist can be effective in improving

nocturnal cough in asthmatic patients. Furthermore, monitoring not only airway inflammation but also nighttime CoFr may offer better management options for evaluating therapeutic response in asthmatic patients.

There are some limitations in the current study. First, nonasthmatic patients had a variety of causes of cough. Each respiratory condition may have its own CoFr pattern. In addition, we studied a small number of patients when evaluating changes in CoFr patterns before and after the appropriate treatment of cough. Thus, although there was still a significant difference, the difference in nighttime CoFr patterns between the asthmatic patients and nonasthmatic patients may have been underestimated. To date, there has been little evidence in CoFr patterns in various respiratory conditions including asthma. Further randomized placebo control studies as well as validation studies with a large sample size are necessary to confirm our findings. Secondly, inhaled drugs for asthma treatment may influence changes in the CoFr pattern. All asthmatic patients were treated with inhaled corticosteroid and long-acting β_2 -agonist. Although our results are preliminary, to our knowledge, this is the first report to show the time course of cough improvement in patients with and without asthma. Further prospective studies with placebo-control arms may support our findings. Finally, we examined the bronchial hyperresponsiveness test and ACT with a small number of patients, and this may lead to a selection bias. However, we believe that this influence on CoFr would be small

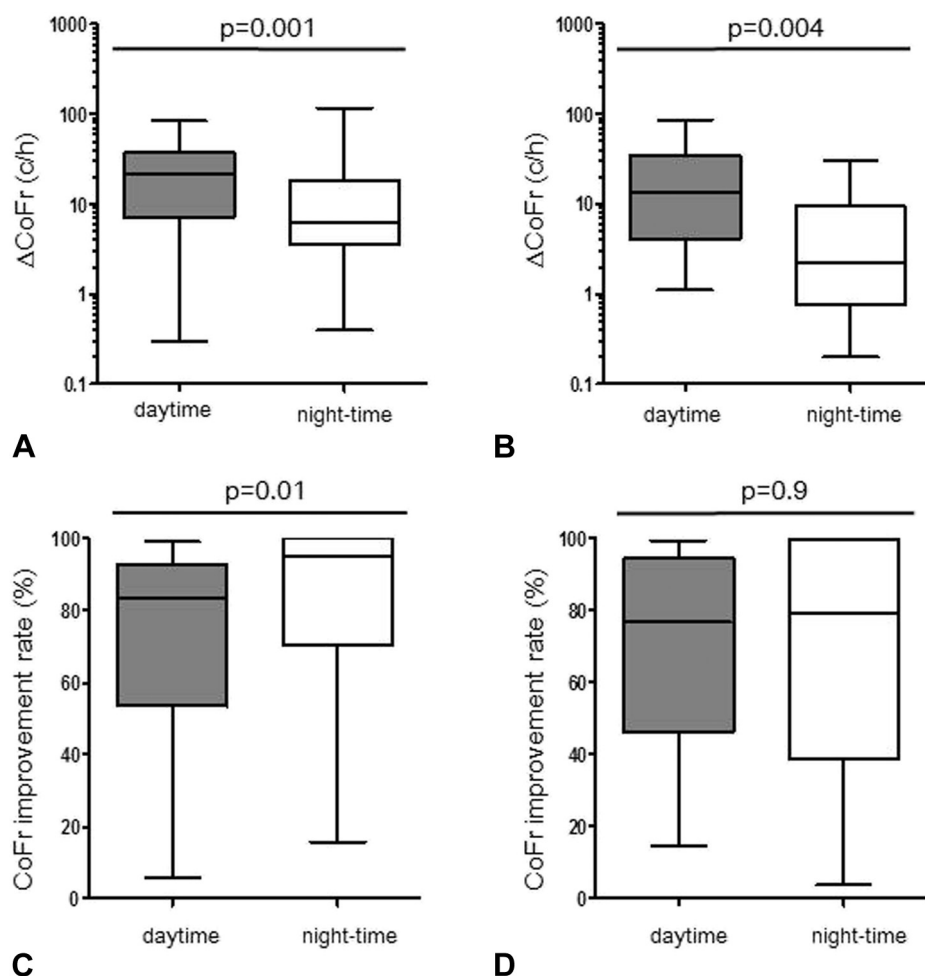


FIGURE 4. Comparisons of changes in cough frequency (CoFr) before and after treatment (ΔCoFr) between daytime and nighttime in the asthmatic patients (A) and in the nonasthmatic patients (B). Comparisons of CoFr improvement rate during daytime and nighttime in the asthmatic patients (C), and in the nonasthmatic patients (D). The thick bar is the median value and the shaded box represents the interquartile range.

because there were no significant differences in CoFr between patients who underwent the tests and those who did not.

In conclusion, nocturnal CoFr in asthmatic patients, which can be associated with bronchial hyperresponsiveness, is different from that in nonasthmatic patients. CoFr monitoring, especially nocturnal CoFr monitoring, may provide unique and valuable information on making an early prediction of the therapeutic effect in asthmatic patients. Further studies with a larger sample size and longer follow-up periods are required to verify our findings.

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manuscript, and approved the final version of the manuscript. SS, MU, YSu, MR, NW, MS, TKa, TU, RT, TKo, KH, HM, TN, KK, and YT recruited patients, interpreted the data, and approved the final version of the manuscript. MM and YSh interpreted the data, critically revised the manuscript, and approved the final version of the manuscript.

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