Original Article

Bronchial asthma with normal forced expiratory volume in 1 second (FEV1) compared with low FEV1

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Background: Cough variant asthma (CVA) is characterized by cough as a sole symptom and normal pulmonary function. However, it is unclear whether CVA really common among asthmatic patients with normal forced expiratory volume in 1 second (FEV1). The aim of this study was to evaluate the incidence of cough alone symptom among the subjects with normal FEV1 and to evaluate their differences from ordinary asthmatic subjects.

Methods: We defined normal FEV1 as ≥90% predicted based on the article of Kotti GH. Of the patients with normal FEV1, we chose subjects without wheeze, and the duration of cough was not to ask, since the symptoms often occurred with acute exacerbation and timing of visiting a doctor depended on each patient's perception. Test for airway hyperresponsiveness was not performed in this study. Visual analogue scale (VAS) scores for cough and dyspnea, FEV1, and fractional exhaled nitric oxide (FeNO) responsiveness to inhaled corticosteroid (ICS)/long-acting beta2 agonist (LABA) treatment were compared in patients with normal FEV1 and with low FEV1 <90%. Correlations of changes in symptoms with changes of FEV1, FeNO, peripheral eosinophil count, and serum immunoglobulin E (IgE) at single time point were also examined in each group and in overall patients.

Results: The participants were 329 physician-diagnosed treatment-naive patients with asthma who were divided into 187 in normal FEV1 and 142 in low FEV1 groups. Cough without dyspnea was present in 16 patients (8.6%) in the normal FEV1 group, suggesting candidates for CVA in this analysis were quite few. Improvement in symptoms after treatment was similar between both groups. But VAS scores of dyspnea were still higher in the low FEV1 group. The degree of improvement in FEV1 after ICS/LABA treatment was less in the normal FEV1 group than in the low FEV1 group, but was still evident. Peripheral eosinophil count, serum IgE, and FeNO values before treatment were lower in the normal FEV1 group. In overall patients, improvements of symptoms after treatment were significantly correlated with FEV1 changes. Improvement of dyspnea was also significantly related to peripheral eosinophil count and change of FeNO, whereas improvement of cough was not related to these T helper 2 (Th2) response markers.

Conclusions: Candidates for CVA among the patients with asthma with predicted FEV1 ≥90% were few. Participants with normal FEV1 respond well to ICS/LABA treatment for improvement of symptom. The change of FEV1 after treatment, and the pre-treatment blood eosinophil count, serum IgE, and FeNO were lower in normal FEV1 cases than in low FEV1 cases. These observations suggest asthmatic patients with normal FEV1, including candidates for CVA having just common mild asthma. In overall participants, symptoms of cough and dyspnea were similar, but were not identical in relation to the Th2 background.

Keywords: Cough variant asthma (CVA); normal forced expiratory volume in 1 second (normal FEV1); mild asthma

Submitted May 26, 2024. Accepted for publication Jul 19, 2024. Published online Aug 30, 2024.
doi: 10.21037/jtd-24-868
View this article at: https://dx.doi.org/10.21037/jtd-24-868

Introduction

Cough variant asthma (CVA) is considered to be the most common cause of chronic cough in Japan and China (1,2). Awareness of CVA began with the first description of this condition by Corrao *et al.* in 1979 (3). This report included six patients with chronic cough as the sole presenting manifestation, with normal pulmonary function, but with a hyperreactive airway to methacholine (3).

In 2024 edition of the Global Initiative for Asthma (GINA) global strategy for asthma management and prevention, information about CVA was updated but fragmented and CVA is still hardly an acceptable situation (4). The Japanese Respiratory Society (JRS) published diagnostic guidelines for CVA in 2005, 2012, and 2019 (5-7), which were modified from the description of Corrao's article. These guidelines defined CVA as a phenotype of asthma with cough as a sole symptom without wheezing or dyspnea, accompanied with normal or near-normal pulmonary function, mild airway hyperresponsiveness, and effectiveness of bronchodilators.

In the 2nd and 3rd editions of the JRS guidelines published in 2012 and 2019, the diagnostic criteria for CVA were only two, persistent cough lasting at least 8 weeks without wheeze, and good responsiveness to a bronchodilator such as a beta-agonist (6,7). The guidelines also noted for reference, but not as a requirement for diagnosis, that the disease may be accompanied by peripheral blood eosinophilia or eosinophilia in the sputum, a high fractional exhaled nitric oxide (FeNO) level, the presence of airway hyperresponsiveness, and changes in the intensity of cough symptoms throughout the day or seasons. Surprisingly, however, there is no mention of cough as the only symptom nor normal pulmonary function in the JRS diagnostic criteria.

In addition, it is uncertain that CVA is really common in Japan, since the small number of asthma patients had with cough as a sole symptom in our previous study (8).

Therefore, we focused the clinical presentation of asthma with normal pulmonary function. More troubling, normal range for pulmonary function, particularly for forced expiratory volume in 1 second (FEV1) and peak expiratory flow (PEF), are not specified in JRS guidelines.

In general, 80% predicted of FEV1 was the cutoff point for normal or near-normal values. However, the Asthma Prevention and Management Guidelines of the Japanese Society of Allergology in 2021, the only asthma treatment guidelines in Japan described degree of severity of asthma with FEV1 ≥80% as "mild" not "normal" (9). Hence, we analyzed retrospectively clinical presentations of asthmatic

Highlight box

Key findings

- There were few with cough as a sole symptom among patients with asthma with normal forced expiratory volume in 1 second (FEV1). Patients with normal FEV1 responded to inhaled corticosteroid (ICS)/long-acting beta2 agonist (LABA) treatment for improvement of symptoms of cough and dyspnea, similarly to patients with low FEV1. Symptomatic improvement of cough and dyspnea after ICS/LABA treatment was correlated with changes of FEV1 with statistically significance both in subjects with normal FEV1 and with low FEV1.
- A difference of perception of cough and dyspnea in relation to T helper 2 (Th2) background was found in all patients in the study.

What is known and what is new?

- Cough variant asthma (CVA) is the most common cause of chronic cough in Japan and China. However, the two diagnostic criteria for CVA in the Japanese Respiratory Society guidelines are also applicable to ordinary bronchial asthma.
- An analysis of asthmatic patients with normal FEV1, in which candidates for CVA are included, showed a few patients with cough as a sole symptom. The subjects with normal FEV1 had symptoms that respond well to treatment, mild responsiveness of FEV1, and a mild Th2 status.

What is the implication, and what should change now?

- Handling of the term "CVA" differs among academic societies in Japan. The Asthma Prevention and Management Guidelines of the Japanese Society of Allergology does not mention CVA as the most frequent subtype of asthma in adults.
- Universal consistency of the CVA concept is required in clinical diagnostic guidelines for asthma and asthma-related conditions.

patients without wheeze, having a predicted FEV1 ≥90% as normal FEV1, as candidate for CVA in this study (10). We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-868/rc).

Methods

Selection of patients

This was a retrospective case-control study performed at a single private clinic. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Joint Ethical Review Board (No. 20231117-25S053) and individual consent for this retrospective analysis was waived.

From August 2018 to July 2020, 548 participants were enrolled according to the following inclusion criteria: diagnosis of asthma made their first visit, no past or present wheeze auscultated, and treatment-naïve or no inhaled corticosteroid (ICS), short-acting β2 agonists (SABAs) or long-acting beta2 agonists (LABAs) taking for at least 3 months before the first evaluation.

All enrolled participants were confirmed no upper respiratory infection, nor abnormal findings indicative of cough etiology on a chest radiograph at the initial visit. In addition, negative salivary polymerase chain reaction (PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was obtained during the pandemic. Diagnosis of asthma was based on identifying both variable respiratory symptoms such as cough, dyspnea, and the presence of expiratory airflow limitation (4). Proof of expiratory airflow limitation was made if any of the following three things: low PEF (<80% predicted), positive bronchodilator response, or concaved pattern of flow volume curve, especially in case of patients with predicted FEV1 ≥90% (normal FEV1) (11,12).

In this study, evaluation of airway hyperresponsiveness was not performed. The period of cough or other respiratory symptoms was not to ask. Since the health care system allows free access to medical facilities in Japan, and the appearance or flare-up of symptoms was often associated with an acute exacerbation of asthma, and no patient waited 8 weeks to see a doctor in real clinical setting. Many patients stop coming to the clinic when their symptoms improve, even though they are educated about the necessity for continued treatment, and they come back when symptoms appear again.

Visual analogue scale (VAS) scores for cough and dyspnea, spirometry, and FeNO data were obtained at the first visit as baseline values. The patients were asked to visit as soon as possible after 1-month ICS/LABA treatment (fluticasone propionate/salmeterol at 250/50 μg twice a day or budesonide/formoterol at 160/4.5 μg twice a day) for a second evaluation of VAS, spirometry, and FeNO. Patients whose second visit was more than 2 months from the baseline evaluation were excluded from the study. Peripheral blood eosinophil counts and immunoglobulin E (IgE) levels were used from the closest time points (3 months in most) before the initial visit or at the initial visit.

VAS

The VAS is a horizontal line (100 mm) labeled with "no symptom" on the left (0 mm) to "most extreme symptom ever experienced" on the right (100 mm). The patient was asked to indicate scores for cough and dyspnea perceived in 1 week prior to the baseline evaluation or since the symptoms appeared in cases with symptoms lasting less than 1 week before the evaluation. At the evaluation after treatment, VAS scores were obtained for the week before the evaluation. The patients did not know the results of spirometry before completing the VAS scores.

Spirometry

Spirometry was conducted with a Microspiro HI-801 (Nihon Koden-Chest Inc., Tokyo, Japan) following instructions in the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines, and the highest forced vital capacity (FVC), FEV1, and FEV1/FVC ratio were taken (13). For FEV1, FVC, vital capacity (VC), and FEV1/FVC ratio, the spirometric reference values were calculated from equations using the lambda-mu-sigma (LMS) methods for Japanese patients (14). The PEF was measured and is presented as absolute values and percent predicted values (% predicted) (15).

The % changes of FEV1 from baseline were calculated by subtracting the baseline value from the post-treatment value and then dividing the difference by the baseline value, indicating a bronchodilator response. A positive response was defined as an increase in FEV1 of >200 mL and a >12% change from baseline after ICS/LABA treatment for 1 month. FeNO was measured with NO Breath (Bedfont Scientific, Maidstone, UK) and the average of duplicate measurements (or triplicates in a case with a difference between the two measurements >10 ppb) was recorded.

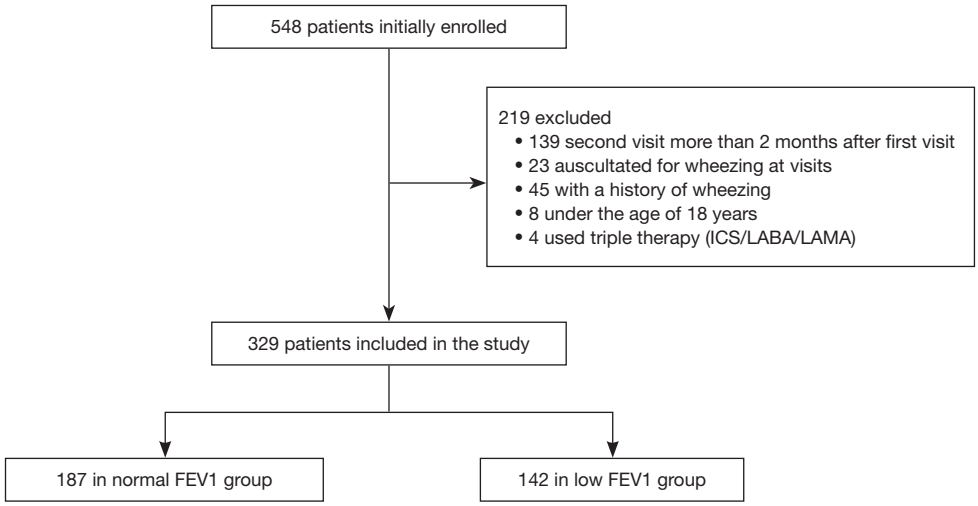

Figure 1 Disposition of the study population. ICS, inhaled corticosteroid; LABA, long-acting beta2 agonist; LAMA, long-acting muscarinic agent; FEV1, forced expiratory volume in 1 second.

Statistical analysis

Quantitative variables were shown as medians [25th–75th interquartile range (IQR)]. VAS scores for cough and dyspnea and spirometric parameters, peripheral eosinophil count, serum IgE, and FeNO values were compared between the normal FEV1 and low FEV1 groups by Mann-Whitney *U* test. Correlation coefficients for changes of VAS scores with changes of absolute FEV1, peripheral eosinophil counts, serum IgE, and FeNO values were evaluated by non-parametric Spearman analysis. All analyses were performed using Graphpad Prism ver. 6 (Graphpad Software, Inc., San Diego, CA, USA), with P<0.05 taken to indicate a significant difference.

Results

Comparison of VAS scores for cough and dyspnea

Of 548 potential participants, 219 were excluded from the study because of not visiting within 2 months after the first visit, past or present wheeze, under the age of 18 years, or prescription of triple therapy (*Figure 1*). Of 329 participants analyzed in this study, 187 had % predicted FEV1 ≥90% (normal FEV1 group) and 142 had % predicted FEV1 <90% (low FEV1 group).

At the initial evaluation, cough without dyspnea was present in 16 patients (8.6%) in the normal FEV1 group and 11 patients (7.7%) in the low FEV1 group. These findings demonstrated that the cases of cough alone in normal FEV1 group was minimal, and that cough without dyspnea can also occur in patients with reduced FEV1.

At baseline, VAS scores [median (25th–75th IQR)] for cough and dyspnea were significantly lower in the normal FEV1 group than in the low FEV1 group [44.9 (17.4–71.1) *vs.* 64.8 (33.4–77.2), P=0.008 for cough; 35.6 (11.9–60.1) *vs.* 49.8 (22.1–67.8), P=0.004 for dyspnea], indicating milder symptoms in normal FEV1 cases (*Figure 2*). Clearly, cough symptoms are not only associated with patients with CVA.

After inhaler treatment, VAS scores for cough decreased to a similar degree in the normal and low FEV1 groups [12.7 (3.0–34.6) *vs.* 13.7 (3.7–37.7), P=0.52]. Dyspnea also improved in both groups, but VAS scores were still higher in the low FEV1 group [11.6 (0.6–29.5) *vs.* 15.9 (5.0–39.1), P=0.01] (*Figure 2*). Thus, cough symptoms and dyspnea were not similarly improved in low FEV1 cases.

Comparison of FEV1 values

The baseline % predicted FEV1 values were all >90% in the normal FEV1 group (*Table 1*). After treatment, both groups showed improvement of FEV1. An evaluation of changes (Δ) in FEV1 in absolute spirometric parameters from baseline to after treatment showed bronchodilator responses of 70 mL (–20 to 170 mL) for ΔFEV1 and 2.8% (–0.7% to 6.2%) for % change from baseline FEV1 in the normal FEV1 group, and larger responses of 165 mL (2 to 378 mL) for ΔFEV1, and 7.8% (–1.0% to 18.2%) for % change from baseline FEV1 in the low FEV1 group. Both changes were

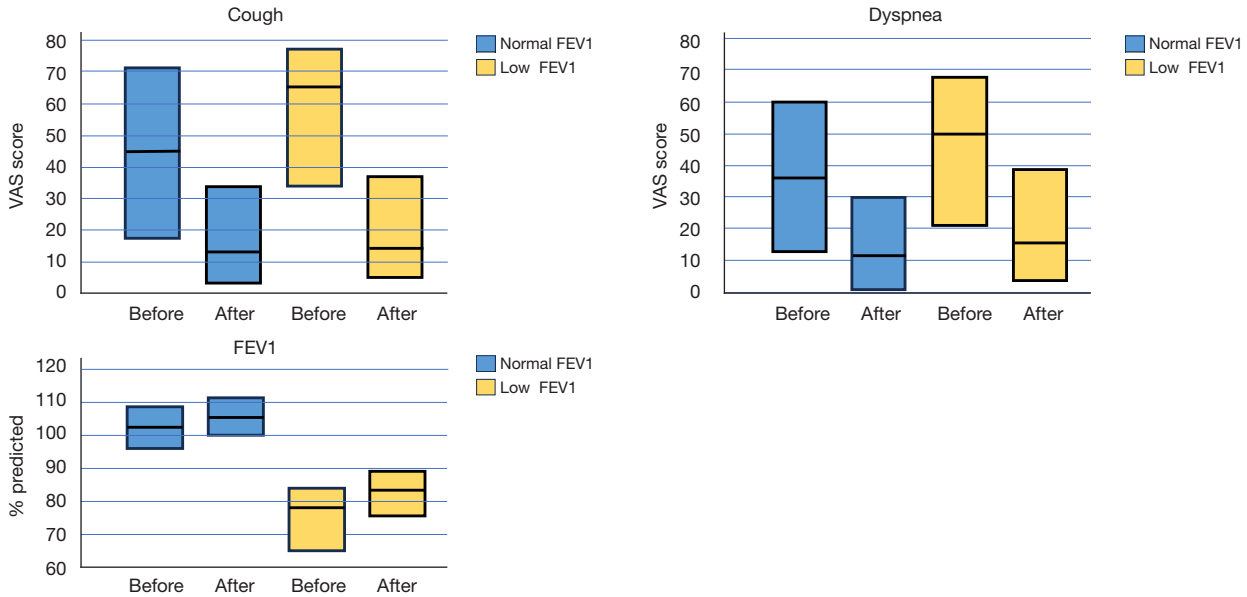

Figure 2 VAS scores for cough (upper left panel), dyspnea (upper right panel), and FEV1 % predicted values (lower left panel) before and after 1-month ICS/LABA treatment in the normal FEV1 and low FEV1 groups. Box plots show the first (lower) quartile, median, and third (upper) quartile. VAS, visual analogue scale; FEV1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta2 agonist.

significantly greater in low FEV1 cases (both P<0.001). A definitive positive bronchodilator response occurred in 9/187 patients (4.8%) in the normal FEV1 group, and in 54/142 (38%) in the low FEV1 group. FVC, VC, and FEV1/FVC values are shown in *Table 1*.

Peripheral eosinophil count, serum IgE, and FeNO

Peripheral eosinophil counts, serum IgE levels, and FeNO were used to evaluate the disease status in the two groups, as surrogate markers of T helper 2 (Th2) inflammation in bronchial asthma (16). Peripheral eosinophil count and serum IgE were significantly lower in the normal FEV1 group, but the difference for IgE (P=0.02) was less than that for the peripheral eosinophil count (P=0.004) (*Table 1*). FENO was slightly lower in normal FEV1 cases before treatment (P=0.01), but did not differ significantly between the groups after treatment (P=0.09) (*Table 1*). ΔFeNO were also similar [normal FEV1 −1.5 (−12.8 to 4.5) *vs.* low FEV1 −3.25 (−14.5 to 6.2) ppb, P=0.66].

Correlations between symptoms and FEV1

ΔCough and Δdyspnea were correlated with ΔFEV1 in the normal FEV1 group (*Table 2*). Correlations of symptomatic improvement of both cough and dyspnea with ΔFEV1 were also observed in the low FEV1 group (*Table 2*). In these analyses, it is noteworthy that symptomatic improvement in normal FEV1 cases was linked to the improvement of FEV1, as observed in low FEV1 cases.

Correlations between symptoms and eosinophil count, FeNO, and IgE

Correlations of symptomatic improvement with surrogate disease markers (peripheral eosinophil count, serum IgE, and FeNO) were evaluated. In normal FEV1 cases, neither Δcough nor Δdyspnea were correlated with any of these markers (*Table 2*). In low FEV1 cases, Δdyspnea was correlated with peripheral eosinophil count, but there were no significant correlations between symptoms and the other disease markers (*Table 2*).

Symptomatic correlations in overall patients

ΔCough in all patients (n=329) was strongly correlated with ΔFEV1 (r=−0.2160, P<0.001), but not with peripheral eosinophil count (r=−0.08855, P=0.11), serum IgE (r=0.0842, P=0.13) or ΔFeNO (r=0.1052, P=0.057) (*Figure 3*). ΔDyspnea also had a clear correlation with ΔFEV1

Table 1 Characteristics of patients in the normal FEV1 and low FEV1 groups

Items	Normal FEV1	Low FEV1	P value
Number	187	142	
Age (years)	42 [35–51]	40 [31–58.5]	0.66
Gender (female:male)	115:72	89:53	0.83
Smoking (NS:ES:SM)	129:44:14	95:32:15	0.79
FEV1 absolute (L)			
Baseline	2.84 [2.54–3.50]	2.19 [1.64–2.53]	<0.001
After treatment	2.93 [2.58–3.60]	2.30 [1.82–2.76]	<0.001
FEV1 % predicted			
Baseline	102.3 [95.6–108.7]	78.6 [65.7–84.5]	<0.001
After treatment	105.3 [99.6–111.1]	83.7 [76.2–89.5]	<0.001
VC absolute (L)			
Baseline	3.42 [2.95–4.21]	2.61 [2.06–3.26]	<0.001
After treatment	3.51 [3.02–3.63]	2.88 [2.34–3.55]	<0.001
VC % predicted			
Baseline	98.4 [90.9–108.2]	77.5 [66.2–89.6]	<0.001
After treatment	101.7 [92.3–111.9]	85.5 [73.3–96.3]	<0.001
FVC absolute (L)			
Baseline	3.44 [2.99–4.15]	2.76 [2.17–3.38]	<0.001
After treatment	3.40 [2.99–4.27]	2.85 [2.25–3.47]	<0.001
FVC % predicted			
Baseline	102 [96–110]	81.9 [73.8–91.5]	<0.001
After treatment	103.5 [96.5–108.4]	84.9 [77.5–94.8]	<0.001
FEV1/FVC ratio			
Baseline	0.84 [0.79–0.88]	0.77 [0.69–0.85]	<0.001
After treatment	0.86 [0.82–0.89]	0.81 [0.74–0.87]	<0.001
PEF absolute (L/s)			
Baseline	6.36 [5.47–7.63]	4.48 [3.77–5.79]	<0.001
After treatment	6.90 [5.81–8.59]	5.34 [4.22–6.59]	<0.001
PEF % predicted			
Baseline	78.2 [67.7–87.7]	55.0 [45.6–65.4]	<0.001
After treatment	83.9 [72.8–94.2]	65.4 [52.4–78.6]	<0.001
Eosinophil count (/μL)	129.6 [91.3–222]	194.6 [81.7–343.2]	0.004
IgE (IU/mL)	79.1 [24.7–201.5]	116 [41.9–339.3]	0.02
FeNO (ppb)			
Baseline	18 [10–32]	24 [11–46]	0.01
After treatment	16.5 [9.5–25.6]	18.0 [9.5–37]	0.09

Values are median [25th–75th IQR] or number. FEV1, forced expiratory volume in 1 second; NS, never smoked; ES, ex-smoker who has quit for at least 3 years; SM, current smoker; VC, vital capacity; FVC, forced vital capacity; PEF, peak expiratory flow; IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide; IQR, interquartile range.

Table 2 Correlations of changes in symptoms with FEV1, eosinophil, IgE, and FeNO

Parameters	Changes	ΔCough *vs.*		ΔDyspnea *vs.*	
		r	P	r	P
Normal FEV1 group					
ΔCough (mm)	−19.5 (−45.4 to −0.6)	–	–	–	–
ΔDyspnea (mm)	−11.2 (−38.8 to 0)	0.5074	<0.001†	–	–
ΔFEV1 (mL)	70 (−20 to 170)	−0.2028	0.005†	−1.501	0.04†
Eosinophil count (/μL)	129.6 (91.3 to 222)	−0.09114	0.22	−0.4462	0.54
IgE (IU/mL)	79.1 (24.7 to 201.5)	0.1374	0.06	0.0443	0.55
ΔFeNO (ppb)	−1.5 (−12.8 to −4.5)	0.03031	0.68	0.1038	0.16
Low FEV1 group					
ΔCough (mm)	−35.9 (−59 to −4.7)	–	–	–	–
ΔDyspnea (mm)	−16.7 (−44.1 to −0.55)	0.6296	<0.001†	–	–
ΔFEV1 (mL)	165 (20 to 378)	−0.214	0.01†	−0.2896	0.001†
Eosinophil count (/μL)	194.6 (81.7 to 343.2)	−0.05849	0.49	−0.199	0.02
IgE (IU/mL)	116 (41.9 to 339.3)	0.03489	0.68	−0.08939	0.29
ΔFeNO (ppb)	−3.3 (−14.5 to −6.2)	0.1979	0.02†	0.1198	0.16

Values are median (25th to 75th IQR). †, statistically significant values. "ΔCough *vs.*"/"ΔDyspnea *vs.*" means Δcough/Δdyspnea *vs.* each parameter in the lines below. FEV1, forced expiratory volume in 1 second; IgE, immunoglobulin E; FeNO; fractional exhaled nitric oxide; Δ, changes; IQR, interquartile range.

(r=−0.2123, P<0.001) and was correlated with peripheral eosinophil count (r=−0.1249, P=0.02) and ΔFeNO (r=0.1100, P=0.046), but not with serum IgE (r=−0.01593, P=0.77). FeNO values before treatment (n=329) strongly correlated with peripheral eosinophils counts (r=0.4269, P<0.001) and IgE levels (r=0.2759, P<0.001) (data not shown). Unlike the results in each group, Δdyspnea and ΔFeNO had a significant correlation in all patients (r=0.1100, P=0.046). These findings show that cough and dyspnea are associated with FEV1, but may have different associations with peripheral eosinophil count and/or FeNO.

Discussion

Diagnosis of cough as CVA is often made without a pulmonary function test and CVA is viewed as a distinct form of ordinary bronchial asthma. The 2nd and 3rd editions of the JRS guidelines have simple diagnostic criteria for CVA requiring persistent cough for at least 8 weeks without wheeze, and a good response to a bronchodilator such as a beta-stimulant (6,7). These guidelines are more objective than earlier versions, but may also encourage an inaccurate diagnosis. Why does the JRS assume cough period of 8 weeks or more? JRS may position CVA as a chronic cough disease, but the appearance of asthma symptoms usually means acute exacerbation. Timing of visiting doctors would depend on each patient's perception even within a week. The requirement for a good response to a bronchodilator is based on the results in Irwin *et al.* (17), but it is unclear if this is specific for CVA. In the current study, pre-treatment VAS scores for cough and dyspnea were lower in normal FEV1 cases than in low FEV1 cases, while after treatment, both symptoms improved and reached similar levels in the two groups. These results show that both normal and low FEV1 cases respond to ICS/LABA treatment and have improved symptoms and FEV1. Of note, the VAS score for dyspnea after treatment was still higher than that for cough in low FEV1 cases.

Yancey and Ortega reported that positive bronchial reversibility (responsiveness) to bronchodilators depends on pre-treatment FEV1 (18); that is, cases with % predicted

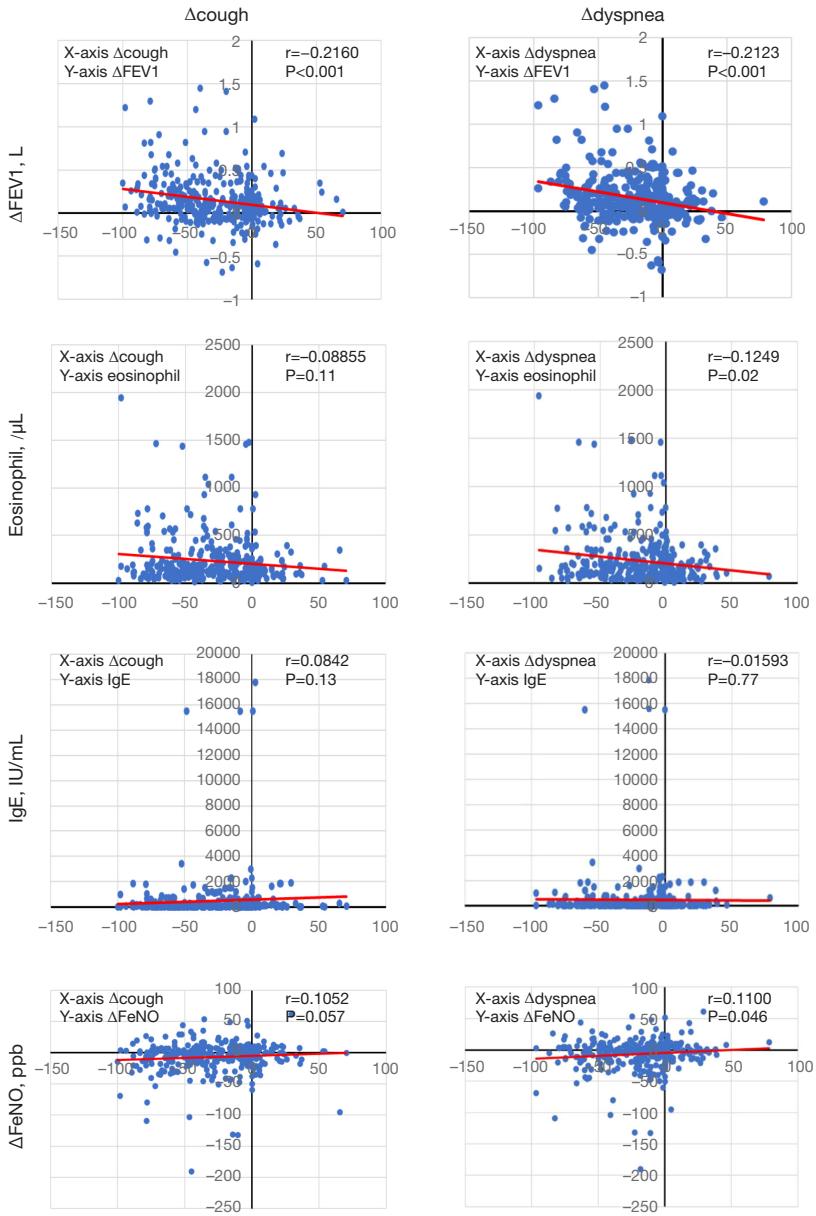

Figure 3 Correlation scatter plots. The X-axis is Δcough (left column) and Δdyspnea (right column). Correlation lines are shown in red. FEV1, forced expiratory volume in 1 second; IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide; Δ, changes.

FEV1 ≥40% to <50%, ≥50% to <60%, ≥60% to <70%, ≥70% to <80%, ≥80% to <90%, and ≥90% to <100% had 42.14%, 34.09%, 27.57%, 22.68%, 19.43%, and 18.33% reversibility, respectively. This is consistent with our observation of reduced FEV1 responsiveness after LABA/ICS inhalation in normal FEV1 cases compared to low FEV1 cases, and the inverse correlation with baseline FEV1.

The difficulty with the JRS guidelines for diagnosis of CVA may be due to differences in the profiles of our patients and those in the first description of CVA by Corrao *et al.* (3). We did not examine hypersensitivity to methacholine, but this is not a concern because the patients in Corrao *et al.* and our normal FEV1 cases shared the common denominator of no decline in pulmonary function tests. By analyses of symptoms and FEV1 before and after ICS/LABA treatment, there was few patients with cough as only symptom, candidate for CVA among the patients

with normal FEV1. It is sufficient to diagnose the patients with normal FEV1, including candidate subject for CVA as mild asthma with an increase in peripheral eosinophil count and serum IgE, even though the use of mild asthma is up for debate (4,19). Moreover, it is important to note that even mild asthma shows improvement in symptoms and FEV1 in response to ICS/LABA treatment. The Asthma Prevention and Management Guidelines of the Japanese Society of Allergology in 2021 in Japan that do not mention CVA as the most frequent subtype of asthma in adults, and a paragraph on CVA appears only in the miscellaneous section (9,20). Thus, there is a lack of consistency among guidelines for asthma published by academic societies in Japan.

In a previous study of cough and dyspnea in patients with asthma with a positive bronchodilator response and an increase in FEV1 (≥12%, ≥200 mL) after ICS/LABA treatment (8), we concluded that the perceptions of cough and dyspnea were similar, but not identical, for responders compared to non-responders. The classification of patients in the current study differed from that in the previous study, but the perception of symptoms of cough and dyspnea after ICS/LABA treatment in low FEV1 cases also differed in the current study. In all patients, improvement of cough and dyspnea were strongly correlated with improvement of FEV1.

The most apparent deference in clinical characteristics of CVA from ordinary bronchial asthma is the absence of wheeze. It has been believed that wheeze in asthma is generated at sites of inflammatory bronchial constriction (21). However, there is another possible mechanism of expiratory wheeze in the obstructive lung diseases, that we have suggested based on a simulation study by the use of computational fluid dynamics (CFD) (22) and four-dimensional computed tomography (4D-CT) image analyses (23). The 4D-CT images during maximum forced expiration in emphysema showed that the membranous part of the intra-mediastinal airways such as intra-thoracic trachea, main bronchi, intermediate bronchus was invaginated and the volume reduction of the intra-mediastinal airways was strongly correlated to the FEV1/FVC (23). This finding is caused by the combination of pulmonary over-inflation and fluid dynamical effect of the turbulent airflow (23). The CFD simulation revealed that the protrusion of the tracheal membranous part generated periodic vortex release with the frequency of 300–900 Hz (22). Although etiologies of emphysema and asthma are different, pulmonary over-inflation due to air-trapping is often seen in advanced asthma. Since pulmonary over-inflation is thought to be involved in the mechanism of wheeze, it is not surprising that there is no wheeze in mild asthma or CVA.

There are some limitations in the study, First, we did not perform methacholine challenge test. Second, we did not insist on cough for more than 8 weeks, defined chronic cough. Third, its retrospective nature required use of some blood test results from dates before the initial visit, although most peripheral eosinophil counts and IgE levels were measured at the initial visit.

Recently the interpretation of pulmonary function test is changing (12,24). In statement of 2021 ATS/ERS technical standard, defining normal range of pulmonary function is proposed using the lower limit of normal at the 5th percentile and upper limit of normal at the 95th percentile instead of 80% predicted value or FEV1/FVC ratio <0.7 (12).

Conclusions

Among patients with bronchial asthma with normal FEV1, few patients had cough alone symptom. This suggested candidates diagnosable as CVA based on the JRS guidelines might be minimal. The patients with normal FEV1 responded well to ICS/LABA treatment with regard to symptoms of cough and dyspnea. These patients showed improvement of FEV1 and FeNO, but to a lesser extent than for patients with low FEV1. Peripheral eosinophil counts and serum IgE of patients with normal FEV1 were also lower than those in patients with low FEV1. These findings suggest that real CVA patients in normal FEV1 subjects might be few, and that diagnosis of mild asthma would be sufficient. Cough and dyspnea did differ slightly in responsiveness, with peripheral eosinophil count and FeNO related to improvement of dyspnea, but not to improvement of cough, suggesting different correlations with markers of Th2 inflammation, with dyspnea apparently more likely to be related to eosinophilic inflammation, compared to cough.

Acknowledgments

We appreciate Dr. Haruyo Yamashita for reading the manuscripts of this study and for giving some advice.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the

STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-868/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-868/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-868/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-868/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Joint Ethical Review Board (No. 20231117-25S053) and individual consent for this retrospective analysis was waived.

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Cite this article as: Ohwada A, Kitaoka H. Bronchial asthma with normal forced expiratory volume in 1 second (FEV1) compared with low FEV1. J Thorac Dis 2024;16(9):5580-5590. doi: 10.21037/jtd-24-868