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Original Article

Seasonal Differences in FEV_1 Response to Bronchodilation: A Comparison between Young and Elderly Patients

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S U M M A R Y

Background: The bronchodilation test is used to detect reversible airways obstruction, which is important for diagnosing asthma. Since asthma activity is influenced by seasons, with higher activity in the spring and fall, this study aimed to determine if the FEV_1 response to bronchodilation is season-dependent.
Methods: All enrolled asthmatic patients underwent pulmonary function testing. Bronchodilation was assessed by measuring FEV_1 change (ΔFEV_1) before and after inhalation of fenoterol 0.4 mg delivered by metered-dose inhaler with a spacer.
Results: There were 348 adult patients with positive bronchodilator test ($\Delta FEV_1 > 12\%$ and 200 mL). In the younger population (n = 223 aged < 65 years), the ΔFEV_1 in winter (January–March) was +331.5 ± 119.0 mL (mean ± SD) and +337.6 ± 110.2 mL in summer (July–September). These were significantly less than the results in the other two seasons (April–June, + 398.9 ± 149.1 mL and October–December, + 397.4 ± 183.3 mL; $p = 0.015$). In the elderly (n = 125 aged ≥ 65 years), the ΔFEV_1 throughout the four seasons was similar ($p = 0.410$).
Conclusions: In younger adults, the bronchodilator variabilities are low in winter and summer, suggesting lower sensitivity of the test due to decreased asthma activity during these seasons. Bronchodilation in the elderly is not season dependent.

1. Introduction

Flow-volume spirometry is a reproducible and reliable method for assessing lung function. The bronchodilation test is used to detect reversible airways obstruction, which is important for diagnosing asthma.[1,2] In clinical practice, the recommended spirometric bronchodilation response in adults is an increase of 12% and 200 mL from baseline forced expiratory volume in 1 s (FEV_1).[3,4] The change in FEV_1 (ΔFEV_1) in response to bronchodilation is related to airway hyper-responsiveness and asthma severity, and can be influenced by many factors like age, sex,[5,6] and bronchodilating medication and its mode of delivery.[7,8] Morbidity varies with seasons and is relatively low during summer and winter.[9,10] The severity of clinical symptoms correlates with the degree of airway hyper-responsiveness. However, if the bronchodilation response is season-dependent remains unknown.

Asthma-related morbidity in children has been predominately linked to allergen exposure and seasonal sensitization. Atopy, however, is uncommon in the elderly with asthma. Whether this relationship of seasonal variation persists in the older population is unknown. Thus, this study aimed to evaluate the effects of seasonal differences on FEV_1 changes in response to bronchodilation in patients with positive bronchodilator test. The results were also compared between the younger and elderly populations.

2. Materials and methods

2.1. Subjects and study design

A total of 2781 patients underwent pulmonary function measurements with bronchodilator testing in an out-patient setting at a

Abbreviations: ΔFEV_1, difference between FEV_1; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow.

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tertiary care medical center in Tamsui, Taiwan, between January 2013 and December 2015. Patients were excluded if they were <20 years of age, had poor performance on pulmonary function testing, or had a peak expiratory flow (PEF) < 40% of predicted. All patients with positive bronchodilator test were included and categorized by month. This study was approved by the Institute Board of MacKay Memorial Hospital (16MMHIS032).

2.2. Pulmonary function tests and bronchodilator test

Pulmonary function measurements were performed according to the American Thoracic Society guidelines.[11,12] No bronchodilators, either β-adrenergic agonists or theophylline, were administered within 8 h before the start of the study. All of the patients also underwent spirometry and lung volume measurements using the nitrogen wash-out method (Vmax 22; SensorMedics; Yorba Linda, CA) in the hospital. The predicted and percent-predicted values were calculated for FEV_1, FVC, and the FEV_1/FVC ratio using the reference values recommended by Knudson et al.[13]

Bronchodilator reversibility tests were performed using the largest FEV_1 and FVC from the best of three spirograms recorded on a single-breath bellows spirometer.[11] The subjects then inhaled 0.4 mg of fenoterol (Berotec; Boehringer Ingelheim) using an MDI under the guidance of a well-trained technician. Spirometry was performed and repeated after a 15–20 min delay. A positive bronchodilator response was defined as improvement of the FEV_1 by > 12% and 200 mL compared to baseline during a single testing session.[11] Those with a positive bronchodilator response constituted the study population.

2.3. Statistical analysis

All data were expressed as mean ± SD. Changes in FEV_1 were expressed as absolute and percent changes from baseline. Different variables for the bronchodilator response (ΔFEV_1 in mL and as percentage) were assessed by multiple logistic regression analysis. Analysis of variance (ANOVA), followed by the Fisher's protected least significant difference post hoc test, was used to compare differences in continuous variables among the different age groups. Statistical significance was set at $p < 0.05$. Differences between groups were tabulated and analyzed using the SPSS software (version 16.0; Chicago, IL).

3. Results

3.1. Population sample

A total of 2781 patients underwent pulmonary function measurements by bronchodilator testing during the study period. The response was positive in 348 individuals (223 between 20 and 65 years of age; 125 aged ≥ 65 years), who constituted the study population. According to the month each occurred during the calendar year, individual increases in ΔFEV_1 (bronchodilator response) were shown (Fig. 1).

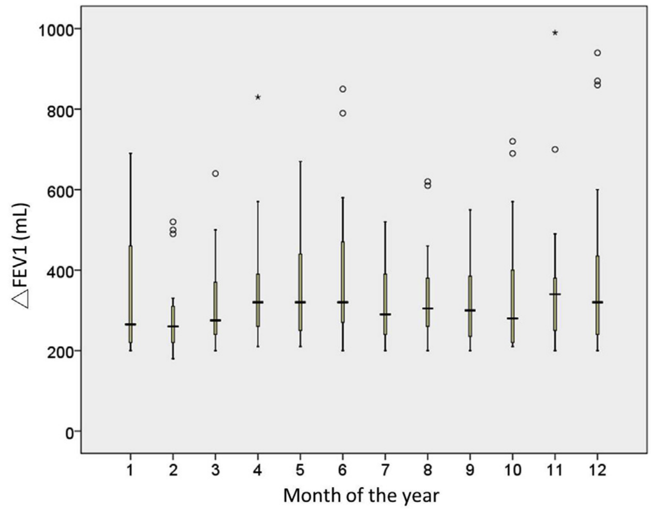

Fig. 1. Boxplots of bronchodilator responses (ΔFEV_1 in mL) of patients presented by month during the calendar year.

There was a trend of seasonal differences in bronchodilation response. The responses significantly increased in April and November. Among the four seasons, no differences were found in the FEV1 values (ml and % of predicted) and FEV1/FVC ratio at baseline spirometry (Table 1). However, the ΔFEV_1 significantly increased in spring (April–June, + 363.2 ± 138.3 mL) and fall (October–December, + 357.2 ± 163.9 mL) than in winter and summer ($p = 0.022$).

In the younger population (age <65 years), there was no significant difference in terms of demographic data or severity of baseline pulmonary function in the four seasons (Table 2). The ΔFEV_1 in winter (January–March) was +331.5 ± 119.0 mL and +337.6 ± 110.2 mL in summer (July–September). Both were significantly less than the results in spring and fall (April–June, + 398.9 ± 149.1 mL and October–December, + 397.4 ± 183.3 mL, respectively; $p = 0.015$) (Fig. 2).

In elderly population (age ≥65 years), there was no significant seasonal difference in baseline pulmonary function (Table 3) and there was only a trend of high ΔFEV_1 in spring, as well as low ΔFEV_1 in winter and summer, but without significant difference ($p = 0.410$) (Fig. 2).

Table 1
Characteristics, baseline values, and bronchodilator response of patients with positive bronchodilator test (n = 348).

Variables	January to March (n = 90)	April to June (n = 98)	July to September (n = 67)	October to December (n = 93)	p[a]
Age, yr	57.9 ± 15.5	58.3 ± 16.5	57.7 ± 16.8	56.6 ± 16.7	0.904
Height, cm	162.0 ± 8.1	162.8 ± 6.9	162.3 ± 8.7	162.2 ± 8.6	0.922
Weight, kg	69.1 ± 15.2	68.1 ± 16.2	69.7 ± 15.7	68.9 ± 13.5	0.933
Baseline spirometry					
FVC, %	87.9 ± 18.2	89.6 ± 19.5	86.4 ± 19.4	93.8 ± 18.6	0.068
FEV_1, %	66.0 ± 18.1	66.1 ± 17.3	68.9 ± 18.0	70.1 ± 17.0	0.306
FEV_1/FVC, %	61.2 ± 13.2	60.5 ± 13.9	65.3 ± 12.1	61.6 ± 13.1	0.116
PEF, %	75.2 ± 24.3	71.2 ± 22.9	74.9 ± 22.6	77.3 ± 23.1	0.329
FEV_1 increase after bronchodilator test					
ΔFEV_1, ml	312.6 ± 111.9	363.2 ± 138.3	320.8 ± 98.0	357.2 ± 163.9	0.022
ΔFEV_1, %	19.9 ± 7.4	23.2 ± 11.8	19.5 ± 7.3	20.7 ± 10.0	0.038

Abbreviations: ΔFEV_1, difference between FEV_1; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow.
Data are expressed as mean ± SD.
[a] Comparison of four groups by ANOVA for continuous variables.

Table 2
Characteristics, baseline values, and bronchodilator response of young patients with positive bronchodilator test (n = 223).

Variables	January to March (n = 59)	April to June (n = 61)	July to September (n = 41)	October to December (n = 62)	P[a]
Age, yr	48.9 ± 10.6	47.8 ± 10.8	47.1 ± 12.0	48.3 ± 13.9	0.903
Height, cm	163.3 ± 8.4	163.2 ± 7.1	162.7 ± 9.4	163.5 ± 8.2	0.977
Weight, kg	71.0 ± 15.8	68.4 ± 17.7	73.7 ± 17.3	70.2 ± 14.1	0.440
Baseline spirometry					
FVC, %	86.0 ± 16.3	86.7 ± 13.6	83.9 ± 14.9	94.1 ± 18.1	0.005
FEV_1, %	65.7 ± 17.8	63.5 ± 12.0	68.1 ± 16.6	69.5 ± 17.7	0.191
FEV_1/FVC, %	63.4 ± 13.3	61.8 ± 13.6	67.5 ± 10.7	61.8 ± 13.5	0.121
PEF, %	78.4 ± 24.9	72.6 ± 18.4	77.8 ± 21.7	78.6 ± 24.2	0.401
FEV_1 increase after bronchodilator test					
ΔFEV_1, ml	331.5 ± 119.0	398.9 ± 149.1	337.6 ± 110.2	397.4 ± 183.3	0.015
ΔFEV_1, %	18.4 ± 64	23.2 ± 12.2	18.4 ± 7.7	21.1 ± 11.4	0.026

Abbreviations: ΔFEV_1, difference between FEV_1; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow.
Data are expressed as mean ± SD.
[a] Comparison of four groups by ANOVA for continuous variables.

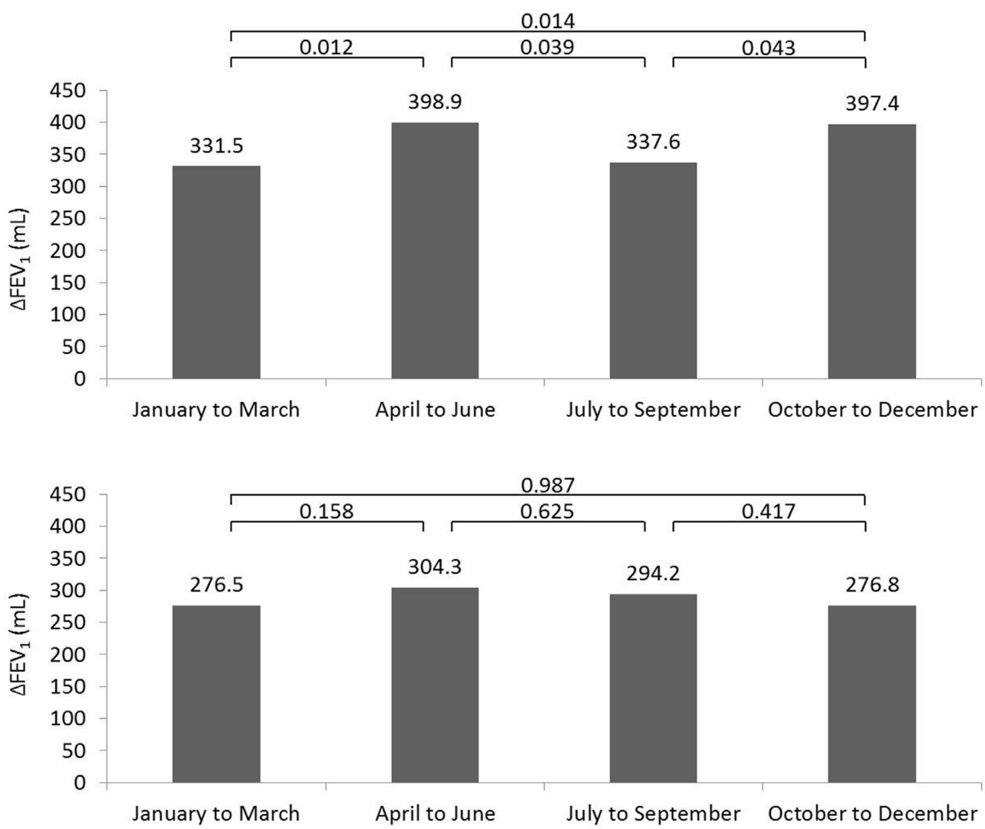

Fig. 2. Bronchodilator responses (ΔFEV_1 in mL) in each of the four seasons of the year among the young (upper) and elderly patients (lower). Data are presented as mean value for each group; $p = 0.015$, by ANOVA for comparison among the four groups in younger adults; $p = 0.410$, by ANOVA for comparison among the elderly; *post hoc* paired comparison achieved significance is shown.

4. Discussion

This study demonstrates that lung function and bronchodilation response differ with months and seasons in the young adult population. The bronchodilator responses to inhaled fenoterol in winter and summer are significantly decreased in the volume of ΔFEV_1 compared to those in spring and fall. This suggests that seasonal differences are an important determinant for the absolute volume of FEV_1 response to bronchodilation. But in the elderly population, seasonal difference may not significantly influence asthma activity and bronchodilation response.

Asthma in the elderly is a growing clinical problem that affects 6–7% of this age-group, but making the distinction between asthma and chronic obstructive pulmonary disease more difficult as patients get older.[14,15] This difficulty is due to several factors: the confounding role of smoking and the physiologic effects of aging on the airways, which renders airway obstruction more resistant to bronchodilation.[16] Elderly asthmatics can be arbitrarily divided on clinical grounds into two groups: "aging asthmatics", or those with asthma since childhood or adolescence, and "late-onset asthmatics", who may present following an infective episode. Hence, it may be hypothesized that aging asthmatics may have season-dependent asthma activity and bronchodilator response, whereas late-onset asthmatics do not have season-dependent response. These can partly explain the current results that bronchodilator response in the elderly is not significantly season-dependent as in the younger population.

Table 3
Characteristics, baseline values, and bronchodilator response of elderly patients with positive bronchodilator test (n = 125).

Variables	January to March (n = 31)	April to June (n = 37)	July to September (n = 26)	October to December (n = 31)	P[a]
Age, yr	75.1 ± 5.9	75.5 ± 6.9	74.5 ± 6.2	73.2 ± 5.6	0.447
Height, cm	159.5 ± 6.9	162.1 ± 6.4	161.6 ± 7.7	159.7 ± 8.9	0.406
Weight, kg	65.4 ± 13.3	67.7 ± 13.6	63.3 ± 10.2	66.3 ± 12.2	0.585
Baseline spirometry					
FVC, %	91.6 ± 21.2	94.4 ± 26.1	90.4 ± 24.6	93.2 ± 19.8	0.913
FEV_1, %	66.6 ± 19.0	70.4 ± 23.3	70.1 ± 20.3	71.2 ± 15.8	0.814
FEV_1/FVC, %	56.9 ± 12.1	58.4 ± 14.4	62.0 ± 13.7	61.3 ± 12.5	0.400
PEF, %	69.0 ± 22.0	68.9 ± 29.0	69.8 ± 23.6	74.8 ± 20.9	0.743
FEV_1 increase after bronchodilator test					
ΔFEV_1, ml	276.5 ± 87.9	304.3 ± 93.4	294.2 ± 68.9	276.8 ± 63.5	0.410
ΔFEV_1, %	22.7 ± 8.4	23.3 ± 11.2	21.2 ± 6.4	19.9 ± 6.6	0.373

Abbreviations: ΔFEV_1, difference between FEV_1; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow.
Data are expressed as mean ± SD.
[a] Comparison of four groups by ANOVA for continuous variables.

It is well known that asthma morbidity is season-dependent.[17] The highest number of emergency department visits for asthma occurs in the fall or winter, and the fewest are in summer.[9] The seasonal variability in asthma activity is likely related to seasonal changes in the prevalence of asthma triggers, which include exposure to allergens, air pollutants, and viral infections.[18,19] None of these peak in Taiwan during summer.[20] The concentration of major air pollutants like nitrogen oxides and sulfur dioxide are also lower in Taiwan during summer compared to any other season.[20,21] Infection rates from respiratory viruses such as respiratory syncytial virus and influenza are lowest in summer. High or low temperature in summer or winter does not increase asthma activity, but the change in temperature in spring and fall does.

In this study, the study hospital is located at the north of Taiwan (Tamsui), where the winter is wet and cold. Nonetheless, the relative hot or cold temperature does not influence asthma activity or bronchodilator response. Thus, the relative absence of asthma triggers during summer and winter produces less asthma activity during these seasons and consequently, lower sensitivity of bronchodilation testing.

The seasonal variability in the sensitivity of exercise testing correlates well with the seasonal variability of asthma activity. The proportion of positive methacholine challenge test shows significant seasonal trend, significantly higher in winter and in spring than in summer.[22,23] Therefore, air pollution and viral infections may well influence bronchial hyper-reactivity (BHR) seasonally and along with allergens, may contribute to seasonal asthma morbidity and mortality peaks. To date, this is the first study to demonstrate a significant seasonal trend in bronchodilator test, especially in the young population, but not in the elderly population.

Some limitations were present in the study. As a retrospective study, we could not record additional clinical data from the patients, such as symptoms, exacerbation events, specific IgE measurements, or medications. However, the present study focused on seasonal effects in bronchodilator responsiveness. As lung function tests were performed only during the time of stable disease, the influence of exacerbation on lung functions would be minimal. Another limitation was the variation in time between inhalation and the second spirometry. The second measurements were generally made 15–20 min after inhalation. These variations might affect the values obtained for bronchodilation response. Nonetheless, the data are robust enough to demonstrate the essentially equivalent lung functions and bronchodilation responses with aging.[24,25]

In conclusion, this study demonstrates that age is an important determinant for lung function and bronchodilation response. In younger adults, the bronchodilator test results in winter and summer are less than in spring and fall, reflecting a lower sensitivity of the test during these seasons due to decreased asthma activity. In contrast, bronchodilation in elderly is not season-dependent.

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