

EFFECTS OF AGE ON 1-SECOND FORCED EXPIRATORY VOLUME RESPONSE TO BRONCHODILATION

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SUMMARY

Background: The bronchodilation test is used to detect reversible airways obstruction, considered important for diagnosing asthma. However, little is known about the effects of age on the bronchodilation response. The aim of this study was to evaluate the effects of age on the bronchodilation response by determining changes in the 1-second forced expiratory volume (FEV₁) in a Chinese population.

Methods: All patients underwent pulmonary function testing to evaluate forced vital capacity, peak expiratory flow, and FEV₁. We assessed bronchodilation by measuring the change in FEV₁ (Δ FEV₁) before and after inhalation of 0.4 mg of fenoterol (two puffs) delivered by a metered-dose inhaler with a spacer.

Results: Of the 1,616 patients tested in the clinic, the 333 (21%) who had a positive bronchodilator test, defined as Δ FEV₁ > 12% and 200 mL, were enrolled in the study. For this population, the Δ FEV₁ was $+360.8 \pm 138.6$ mL (mean \pm standard deviation) or $+21.0\% \pm 9.1\%$. In a multiple linear regression model, the absolute Δ FEV₁ (expressed in milliliters) was independently and negatively predicted by age ($p < 0.001$), and baseline peak expiratory flow ($p < 0.001$), but positively predicted by height ($p < 0.001$).

Conclusion: Age was an important determinant for response to bronchodilation as determined by the absolute change in FEV₁. [International Journal of Gerontology 2009; 3(3): 149–155]

Key Words: asthma, bronchodilators, lung function tests, spirometry

Introduction

Flow-volume spirometry is a reproducible and reliable method for assessing lung function. The bronchodilation test is used to detect reversible airways obstruction, considered to be important for diagnosing asthma^{1,2}. In clinical practice, the criterion for a significant spirometric bronchodilation response in adults is recommended to be an increase in 1-second forced

expiratory volume (FEV₁) of 12% and 200 mL from baseline^{3,4}.

The change in FEV₁ (Δ FEV₁) in response to bronchodilation can be influenced by many factors, including the bronchodilation medication, its mode of delivery, and the type of spirometer used^{5,6}. FEV₁ has been shown to be the best variable for determining the response to bronchodilation in terms of statistical power and reproducibility, but it is dependent on the baseline FEV₁ at the population level⁶. Some previous reports have documented smaller bronchodilation responses in older people and an effect of sex on the response^{7,8}. A low baseline ratio of FEV₁ to forced vital capacity (FVC), or FEV₁:FVC ratio, also reflects airflow limitations and is another determinant of the change in FEV₁ in response to bronchodilation⁹.



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Numerous studies on bronchodilation responses have been published in patients with obstructive ventilatory defects in selected or non-selected populations^{7–10}. Some studies involved asthmatic population samples with reversible obstructive airways, but the concurrent changes in baseline lung function have not been reported in aged populations^{7,8}. Furthermore, South Asian populations have a smaller FEV₁ and Δ FEV₁ by volume and, therefore, are more likely to be classified as having an equivocal response. The aim of this study was to evaluate the effects of age on the distribution and range of the changes in FEV₁ in response to bronchodilation in a group of Chinese patients who had a positive bronchodilator test.

Materials and Methods

Subjects and study design

A total of 1,616 patients underwent pulmonary function measurements with bronchodilator testing in an outpatient setting at a local teaching hospital in Taitung, Taiwan, and a tertiary care medical center in Taipei from January 2006 to December 2008. Patients were excluded if they were <18 years of age, had poor performance on pulmonary function testing, or had a peak expiratory flow (PEF) at <40% of predicted.

All subjects who had a positive bronchodilator test were included and categorized by age (<30, 30–39, 40–49, 50–59, 60–69, and >70 years of age).

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 hours before the start of the study. All patients also underwent spirometry and lung volume measurements using either the nitrogen washout method (Vmax 22; SensorMedics, Yorba Linda, CA, USA) at the Taitung hospital, or a body plethysmograph (Vmax 22 and Autobox 6200; SensorMedics) at the Taipei hospital. Predicted and percent-predicted values were calculated for FEV₁, FVC, and the FEV₁:FVC ratio using the reference values recommended by Knudson et al.¹³.

Bronchodilator reversibility tests were performed using the largest FEV₁ and FVC from the best of three spirograms recorded on a single-breath bellows spirometer¹¹. All subjects then inhaled 0.4 mg (two puffs) of

fenoterol (Berotec; Boehringer Ingelheim, Ingelheim, Germany) using a metered-dose inhaler (MDI) under the guidance of a well-trained technician. Spirometry was performed and repeated after a 15–20 minute delay. A positive bronchodilator response was defined as improvement of the FEV₁ of >12% and 200 mL over baseline during a single testing session. Subjects with a positive bronchodilator response constituted our study population.

Statistical analysis

All data are expressed as mean \pm standard deviation. Changes in FEV₁ are expressed as absolute and percent changes from baseline. Differences between groups were analyzed as appropriate using the Pearson's χ^2 test for categorical variables. Bronchodilator response variables (Δ FEV₁, expressed in milliliters and as percentage) were assessed using multiple logistic regression analysis. Analysis of variance, followed by Fisher's protected least significant difference *post hoc* test, was used to compare differences in continuous variables among the different age groups. A *p* value <0.05 was considered statistically significant. Differences between groups were tabulated and analyzed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA).

Results

Population sample

A total of 1,616 patients underwent pulmonary function measurements with bronchodilator testing during the study period. Of these, the response to bronchodilators was positive in 333 individuals, who thus constituted the study population; of these, 114 (34%) were elderly (age, 60–86 years).

For the population, the mean change in FEV₁ was +360.8 \pm 138.6 mL or 21.0% \pm 9.1%; the mean change in FEV₁ for men was +385.8 \pm 149.2 mL or 21.5% \pm 9.9% and that for women was +326.8 \pm 117.2 mL or 20.7% \pm 8.3% (Table 1). Men had a significantly greater absolute Δ FEV₁ (*p* < 0.001), but the percentage of Δ FEV₁ (% Δ FEV₁; *p* = 0.459) did not differ by sex (Table 1).

In a multiple linear regression model, the absolute bronchodilator response (Δ FEV₁, expressed in milliliters) was independently and negatively predicted by age (*p* < 0.001), weight (*p* = 0.030) and baseline PEF (*p* < 0.001), but positively predicted by height (*p* < 0.001)

Table 1. Patient characteristics, baseline values, and bronchodilator responses in the study population of 333 participants with a positive bronchodilator test*

Variables	Total (n=333)	Population sample		p
		Men (n=212)	Women (n=121)	
Age (yr)	53.3±17.7	56.8±17.9	47.2±15.7	<0.001
Height (cm)	162.0±8.9	165.9±7.9	155.2±6.2	<0.001
Weight (kg)	67.2±13.4	69.7±13.7	62.5±11.2	<0.001
BMI (kg/m ²)	25.6±4.8	25.3±4.6	26.1±5.1	0.145
FVC (% predicted)	81.8±17.9	83.6±20.0	78.8±12.9	0.009
FEV ₁ (% predicted)	68.2±16.6	68.7±18.2	67.6±13.3	0.508
FEV ₁ /FVC	68.6±10.7	66.5±10.8	72.4±9.7	<0.001
FEF _{25-75%} (% predicted)	43.9±21.9	42.4±21.6	47.0±23.3	0.070
PEF (% predicted)	74.7±19.6	71.6±19.0	80.2±19.9	<0.001
Bronchodilation responses				
ΔFEV ₁ (mL)	360.8±138.6	385.8±149.2	326.8±117.2	<0.001
ΔFEV ₁ (%)	21.0±9.1	21.5±9.9	20.7±8.3	0.459

*Data are expressed as mean ± standard deviation. BMI = body mass index; FVC = forced vital capacity; FEV₁ = 1-second forced expiratory volume; FEF_{25-75%} = forced expiratory flow between 25% and 75% of forced vital capacity; PEF = peak expiratory flow; ΔFEV₁ = change in 1-second forced expiratory volume.

Table 2. Regression coefficients of bronchodilator response (change in 1-second forced expiratory volume, expressed in milliliters) for all participants (n=333) in multiple regression models after adjustment for different variables

Variables	Coefficient (SE)	95% CI	p
Age (yr)	-3.07 (0.49)	-4.04 to -2.10	<0.001
Height (cm)	13.95 (3.75)	6.57 to 21.34	<0.001
Weight (kg)	-9.40 (4.31)	-17.88 to 0.93	0.030
BMI (kg/m ²)	26.33 (11.26)	4.18 to 48.48	0.020
FVC (% predicted)	2.32 (1.97)	-1.55 to 6.19	0.239
FEV ₁ (% predicted)	-1.51 (2.41)	-6.25 to 3.24	0.533
FEV ₁ /FVC	0.29 (2.41)	-4.45 to 5.03	0.896
FEF _{25-75%} (% predicted)	0.65 (0.65)	-0.63 to 1.93	0.319
PEF (% predicted)	-1.11 (0.43)	-1.94 to -0.27	<0.001

SE = standard error; CI = confidence interval; BMI = body mass index; FVC = forced vital capacity; FEV₁ = 1-second forced expiratory volume; FEF_{25-75%} = forced expiratory flow between 25% and 75% of forced vital capacity; PEF = peak expiratory flow.

and body mass index ($p=0.020$; Table 2). However, the percentage changes in FEV₁ were negatively predicted only by the baseline FEV₁:FVC ratio ($p=0.023$) and PEF ($p<0.001$; Table 3).

Trends in lung function by age category

At the baseline pulmonary function test, the elderly patients had significantly smaller FEV₁:FVC ratio ($p<0.001$), forced expiratory flow between 25% and 75% of FVC (FEF_{25-75%}) as a percentage of predicted

($p=0.001$), and PEF as a percentage of predicted ($p<0.001$) than the younger population (Table 4).

Trends in bronchodilation response by age

After inhalation of the bronchodilator, the FEV₁ increased significantly over baseline in both groups (Table 4). The absolute bronchodilator response (ΔFEV₁, expressed in milliliters) was independently and negatively predicted by aging ($p<0.001$; Table 4, Figure 1). The elderly had an insignificantly greater

Table 3. Regression coefficients of bronchodilator response (change in 1-second forced expiratory volume, expressed as percentage) for all participants ($n=333$) in multiple regression models after adjustment for different variables

Variables	Coefficient (SE)	95% CI	<i>p</i>
Age (yr)	-0.03 (0.03)	-0.09 to 0.04	0.399
Height (cm)	0.23 (0.25)	-0.26 to 0.71	0.363
Weight (kg)	-0.46 (0.28)	-1.02 to 0.10	0.106
BMI (kg/m ²)	1.36 (0.74)	-0.10 to 2.81	0.068
FVC (% predicted)	-0.13 (0.13)	-0.39 to 0.12	0.300
FEV ₁ (% predicted)	-0.02 (0.16)	-0.33 to 0.29	0.889
FEV ₁ /FVC	-0.36 (0.16)	-0.67 to -0.05	0.023
FEF _{25-75%} (% predicted)	0.05 (0.04)	-0.04 to 0.13	0.255
PEF (% predicted)	-0.11 (0.03)	-0.17 to -0.06	<0.001

SE = standard error; CI = confidence interval; BMI = body mass index; FVC = forced vital capacity; FEV₁ = 1-second forced expiratory volume; FEF_{25-75%} = forced expiratory flow between 25% and 75% of forced vital capacity; PEF = peak expiratory flow.

bronchodilation response in Δ FEV₁ ($p=0.052$) compared with the young population (Table 4, Figure 2).

Discussion

This study demonstrates that lung function and bronchodilation response were correlated with aging. The elderly were short in height and had a significantly smaller FEV₁:FVC ratio, FEF_{25-75%}, and PEF as a percentage of predicted than the young population. The bronchodilator response to inhaled fenoterol in the elderly was significantly lower in volume of Δ FEV₁ but slightly increased in Δ FEV₁, compared with the young population. This suggests that age is an important determinant for absolute volume of FEV₁ response to bronchodilation.

Some investigators have suggested that spirometry, and particularly assessment of the bronchodilator response, is not uniformly sensitive for the diagnosis of asthma, with sensitivities reportedly ranging from 82–93%, depending on the criteria used for a positive response^{14,15}. Our data suggests that some of the variability in response to inhaled β_2 -agonists can be attributed to age, height, sex, and baseline FVC. So, for example, we found that younger, taller patients who had a larger baseline FVC had a relatively larger improvement in the volume of FEV₁, but a smaller percentage improvement. Similarly, short, older Asian women in our study had a smaller Δ FEV₁ by volume and, therefore, were more likely to be classified as having an equivocal response. Asthma cannot be definitively excluded in such cases.

We found that preexisting airflow limitation in terms of decreased FEV₁:FVC ratio and lung volume was the strongest determinant for bronchodilation responses in the reversible obstructive airway population. Although a larger absolute bronchodilation response was found in men than in women, this phenomenon can be explained by the more frequent findings of airflow limitation (i.e., reduced FEV₁:FVC ratio) and a larger FVC in men^{16,17}. In our participants, we observed a significant negative correlation with age more clearly with the absolute change in FEV₁ and less so with the relative change in FEV₁. This can be partially attributed to the aging-related reduction in FEV₁:FVC ratio and smaller lung volumes found in persons in older age groups^{16,17}. A weak negative correlation of age with change in FEV₁ might also be explained by the diminished coordination and greater fatigue common in elderly patients, resulting more frequently in the decreasing FEV₁ found in bronchodilation test results.

PEF is a measure of maximal expiratory flow that is used to assess qualitative and quantitative effort in spirometry maneuvers^{18–20}. FEV₁ is a measurement of volume in the first second of a spirometry maneuver^{2,4}. Both of these measurements have played an important role in the identification and management of different severities of asthma. FEV₁ is commonly assumed to be partly dependent on PEF on the basis of a high correlation between PEF and FEV₁^{21,22}. Hence, the maximal expiratory work was related to the highest PEF, but the highest PEF was not associated with the largest FEV₁²³. Previous studies have reported only a weak correlation between PEF variability and FEV₁ variability^{22,23}. In our data, there is a trend toward lower PEF and smaller FEV₁

Table 4. Demographic and clinical characteristics of the study participants (n = 333) by age*

	Age of subjects (yr)					p	
	18–29 (n = 44)	30–39 (n = 38)	40–49 (n = 47)	50–59 (n = 63)	60–69 (n = 67)		70–86 (n = 74)
Male to female ratio	24:20	19:19	23:24	32:31	52:15 [†]	62:12 [‡]	<0.001
Height (cm)	166.9 ± 9.7	163.0 ± 9.0 [†]	163.1 ± 9.0 [†]	161.0 ± 9.4 [‡]	160.4 ± 7.8 [‡]	160.3 ± 8.0 [‡]	0.001
Weight (kg)	64.2 ± 15.7	68.3 ± 15.3	70.7 ± 13.9 [†]	70.0 ± 13.4 [†]	66.0 ± 11.1	64.2 ± 11.1	0.023
BMI (kg/m ²)	22.9 ± 4.6	25.8 ± 6.1 [‡]	26.6 ± 4.9 [‡]	27.0 ± 4.6 [‡]	25.7 ± 4.0 [‡]	25.0 ± 4.3 [‡]	<0.001
FVC (% predicted)	82.7 ± 11.5	85.2 ± 13.4	79.4 ± 11.6	78.2 ± 16.1	79.5 ± 17.8	86.6 ± 25.5	0.047
FEV ₁ (% predicted)	74.3 ± 10.5	70.2 ± 15.6	67.3 ± 12.9 [†]	65.3 ± 13.9 [‡]	66.1 ± 16.2 [‡]	68.9 ± 22.9 [†]	0.084
FEV ₁ /FVC	77.5 ± 7.7	69.7 ± 10.3 [‡]	70.9 ± 9.5 [‡]	68.9 ± 9.7 [‡]	67.3 ± 10.9 [‡]	62.4 ± 10.0 [‡]	<0.001
FEF _{25–75%} (% predicted)	57.1 ± 17.9	45.7 ± 20.8 [‡]	45.4 ± 22.6 [‡]	42.0 ± 20.2 [‡]	41.6 ± 22.6 [‡]	38.7 ± 24.0 [‡]	0.001
PEF (% predicted)	78.5 ± 15.1	75.8 ± 18.2	79.9 ± 18.9	80.3 ± 21.9	71.6 ± 19.1	66.7 ± 19.4 [‡]	<0.001
Bronchodilator responses							
ΔFEV ₁ (mL)	473.9 ± 149.9	455.0 ± 158.9	388.1 ± 138.3 [‡]	338.6 ± 120.8 [‡]	321.6 ± 14.5 [‡]	298.4 ± 87.1 [‡]	<0.001
ΔFEV ₁ (%)	17.9 ± 6.7	21.4 ± 10.5	20.0 ± 8.9	20.7 ± 8.5	22.0 ± 10.5 [†]	23.4 ± 9.6 [‡]	0.052

*Data are expressed as mean ± standard deviation; [†]p < 0.05 compared with the younger group (18–29 years); [‡]p < 0.01 compared with the younger group (18–29 years). BMI = body mass index; FVC = forced vital capacity; FEV₁ = 1-second forced expiratory volume; FEF_{25–75%} = forced expiratory flow between 25% and 75% of forced vital capacity; PEF = peak expiratory flow; ΔFEV₁ = change in 1-second forced expiratory volume.

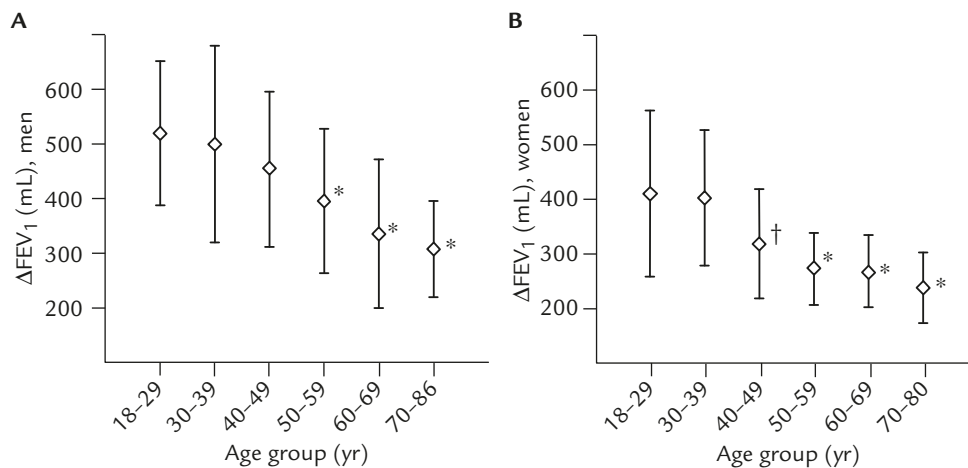


Figure 1. Reduction in volume of bronchodilation response (change in 1-second forced expiratory volume [ΔFEV_1], expressed in milliliters) for: (A) men and (B) women with age. Data are displayed as mean \pm standard deviation. * $p < 0.01$, † $p < 0.05$ compared with the younger group (18–29 years).

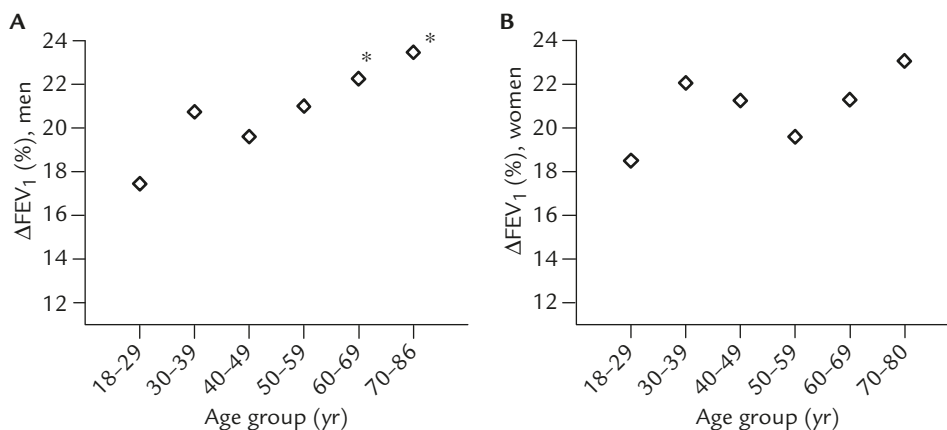


Figure 2. Increase in bronchodilation response (change in 1-second forced expiratory volume [ΔFEV_1] as percentage) for: (A) men and (B) women with age. Data are displayed as mean. * $p < 0.05$ compared with the younger group (18–29 years).

in the elderly participants. However, after bronchodilation, the percentages of ΔFEV_1 or ΔPEF (data not shown) were not correlated with aging. PEF is considered as an expiratory effort, and it seemed to be negatively correlated with aging. On the other hand, the percentage of ΔPEF indicated a reversibility of obstructive airway, and it seemed not to be related to aging.

Inhaled β -adrenergic bronchodilators are cornerstones in the management of asthma². MDI delivery of these drugs has the advantage of convenience, ease of administration, and rapid onset of action. However, MDIs are not without their shortcomings. Many patients, particularly the very young and elderly, have difficulty coordinating inhaler actuation with inspiratory effort^{24,25}. Our research technicians were careful to ensure that the study participants were using the MDI correctly; therefore, caution must be used in generalizing

the results to patients who might have difficulty using the correct technique.

A limitation of this study was variation in the time between inhalation and the second spirometry. Our second measurements were generally made 15–20 minutes after inhalation. The variations in time interval might affect the values obtained for bronchodilation response. However, we believe our data are robust enough to demonstrate the essentially equivalent lung function and bronchodilation responses with aging.

In conclusion, this study showed that age is an important determinant for lung function and bronchodilation response. The elderly were shorter in height and had a significantly smaller $FEV_1:FVC$ ratio and lower PEF as a percentage of predicted values. The absolute bronchodilator response (ΔFEV_1 , expressed in milliliters) was independently and negatively predicted by aging.

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