

# Forced expiratory volumes in 3 s is a sensitive clinical measure for assessment of bronchodilator reversibility in elderly Chinese with severe lung function impairment

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**Purpose:** Sensitively assessing bronchial reversibility by spirometry is difficult in patients with serious airflow limitation and the elderly. Some patients cannot exhale for  $\geq 6$  s to achieve FVC testing criteria. The aim of this study was to assess if FEV<sub>3</sub> could be a more sensitive and an acceptable surrogate for evaluating bronchial reversibility in such patients.

**Patients and methods:** Subjects who had undergone pulmonary function examination in Beijing hospital from July 2003 to April 2015 were included in the study. Patients with FEV<sub>1</sub> < 50% of the predicted value were classified as the severely lung function-impaired group. Correlation between the severity of lung function impairment and changes in FEV<sub>1</sub>, FEV<sub>3</sub> and FVC in response to a bronchodilator was estimated.

**Results:** A total of 7745 tests on elderly subjects with a median age of 71 years were reviewed. The severely lung function-impaired group of 1728 accounted for 22.3% of the total number of subjects. There were significantly more patients in the severely lung function-impaired group who exhibited positive response in FEV<sub>3</sub> or FVC and negative response in FEV<sub>1</sub> after bronchodilator test (FEV<sub>1</sub> negative response but FVC positive response,  $\chi^2=626.97$ ,  $P<0.001$ ; FEV<sub>1</sub> negative response but FEV<sub>3</sub> positive response,  $\chi^2=372.83$ ,  $P<0.001$ ). With the progressive increase in lung function impairment,  $\Delta$ FEV<sub>1</sub> increased and then declined, while  $\Delta$ FVC and  $\Delta$ FEV<sub>3</sub> increased progressively. Changes in FEV<sub>3</sub> or FVC significantly exceeded the change in FEV<sub>1</sub> in the severely lung function-impaired groups ( $P<0.001$ ).

**Conclusion:** In elderly subjects, especially those with severe lung function impairment, FEV<sub>3</sub> combined with FVC is a more effective and sensitive primary clinical outcome measure to detect bronchial reversibility. In subjects who cannot complete  $\geq 6$  s forced expiration and whose FVC is unreliable, FEV<sub>3</sub> combined with FEV<sub>1</sub> might be clinically more valuable in detecting bronchial reversibility.

**Keywords:** airway obstruction, FEV<sub>3</sub>, forced expiratory volume in 3 second, bronchodilator responsiveness, lung function tests, elderly patients

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## Introduction

Therapeutic effectiveness of inhaled drugs in patients with chronic airway inflammatory diseases such as COPD and asthma is usually assessed by the changes in pulmonary function. FEV<sub>1</sub> is the most commonly used indicator of pulmonary function. Clinical trials have revealed that changes in FEV<sub>1</sub> before and after treatment are not sensitive enough to reflect the effect of bronchodilators in patients

with serious airflow limitation, especially the elderly.<sup>1</sup> FVC was reported to be more sensitive than FEV<sub>1</sub> in detecting bronchial reversibility in COPD patients.<sup>2</sup> Patients who did not show bronchial responsiveness in FEV<sub>1</sub> might show changes in lung volume measurements called “volume response”.<sup>3</sup>

According to the American Thoracic Society/European Respiratory Society (ATS/ERS) criteria, FVC testing requires a forced expiratory time of 6 s or a plateau in the volume–time curve.<sup>4</sup> This is often a relatively long time to exhale, especially for patients with severe airway limitation, aged people and patients with diseases such as severe cough and heart failure.<sup>5,6</sup> In a study on elderly population, 25% of the subjects could complete FEV<sub>3</sub> but not FVC.<sup>7</sup> Another study demonstrated that among 2,928 lung function tests only 47% could exhale for <4 s.<sup>6</sup>

The FEV<sub>3</sub> is the rapidly exhaled volume during the first 3 s of a forced expiratory maneuver, which starts at the level of total lung capacity. It is reproducible, needs shorter expiratory effort and provides an exact outcome.<sup>8</sup> Studies have reported that FEV<sub>3</sub> could be considered as a possible surrogate for FVC<sup>9</sup> as well as an alternative to FEV<sub>1</sub>.<sup>10</sup> However, whether FEV<sub>3</sub> can detect bronchodilator responsiveness as sensitively as FVC in the elderly population remains controversial.

In the present study, we studied a large unselected Chinese elderly population presenting to our hospital defined by lung function characteristics in relation to bronchodilator response. We attempted to evaluate the changes in FEV<sub>1</sub>, FVC and FEV<sub>3</sub> in response to a bronchodilator and reveal if changes in FEV<sub>3</sub> post-bronchodilator test could be an acceptable and sensitive indicator to evaluate bronchodilator response in the elderly patients with severe airflow limitation. In addition, we attempted to find some sensitive indicators that would reflect the improvement in lung function accurately in patients who in spite of their best ability could not breathe continuously for 6 s – a problem that needs clinical resolution.

## Materials and methods

Elderly subjects who had undergone pulmonary function examinations in Beijing hospital from July 2003 to April 2015 were analyzed with the following characteristics: age 60 years or older, completion of post-bronchodilator spirometry that included FEV<sub>3</sub> in lung function test.

Measurement of pulmonary function: All subjects underwent pulmonary function tests in Beijing Hospital on a Vmax 622 pulmonary function instrument (Sensormedics, USA) and plethysmograph (Sensormedics, USA) according to pulmonary function test guidelines.<sup>5</sup> Each lung function test was

repeated 3 times and the best value was considered for analysis. All subjects underwent a bronchodilator test which required the administration of 400 µg of salbutamol via metered dose inhaler. Spirometry was repeated 15 mins after short-acting β<sub>2</sub>-agonist administration. Data from patients were collected anonymously. The enrollees were divided into 6 groups according to ERS criteria for categorizing the severity of lung function impairment based on FEV<sub>1</sub>% predicted value:<sup>4</sup> Group A, FEV<sub>1</sub> ≥ 80% predicted value; Group B, 70% predicted value ≤ FEV<sub>1</sub> < 80% predicted value; Group C, 60% predicted value ≤ FEV<sub>1</sub> < 70% predicted value; Group D, 50% predicted value ≤ FEV<sub>1</sub> < 60% predicted value; Group E, 35% predicted value ≤ FEV<sub>1</sub> < 50% predicted value and Group F, FEV<sub>1</sub> < 35% predicted value.<sup>4</sup> Changes (Δ) in FEV<sub>1</sub>, FEV<sub>3</sub> and FVC after the bronchodilator test were expressed in milliliters, percentage of predicted value or percentage of baseline. To minimize any bias due to age, height and weight, ΔFEV<sub>1</sub>, ΔFEV<sub>3</sub> and ΔFVC were also z score normalized. Correlation between lung function impairment and changes in FEV<sub>1</sub>, FEV<sub>3</sub> and FVC after bronchodilator responsiveness test was estimated. The study protocol was approved by the Beijing Hospital ethics committee.

Data was analyzed using the SPSS 17.0 software. Normally distributed data was expressed as  $\bar{x} \pm s$ , and non-normally distributed data was expressed as M (Q1, Q3). Chi-square test was used to compare the relative frequencies of patients among the groups. Mann–Whitney U test was used for comparing data that was not normally distributed.  $P < 0.05$  was regarded as statistically significant.

## Ethics approval and informed consent

The study was conducted in accordance to the Declaration of Helsinki and approved by the ethics committee of Beijing hospital. Informed consents were waived due to the retrospective nature of the study, and all patient data was anonymized.

## Results

In the present study, a total of 7745 tests in subjects aged 60 years or older with a median age of 71 years were reviewed. Out of the total, 61.7% were males (4781) and 38.3% were females (2964). Out of the 7745 patients, 2985 (38.5%) were in Group A, 1129 (14.6%) were in Group B, 1066 (13.8%) were in Group C, 837 (10.8%) were in Group D, 1183 (15.3%) were in Group E and 545 were in Group F (7%). There was no significant difference in age and gender distribution between the groups ( $P > 0.05$ ) (Table 1). In order to facilitate statistical analysis, Groups E and F were classified as severely lung

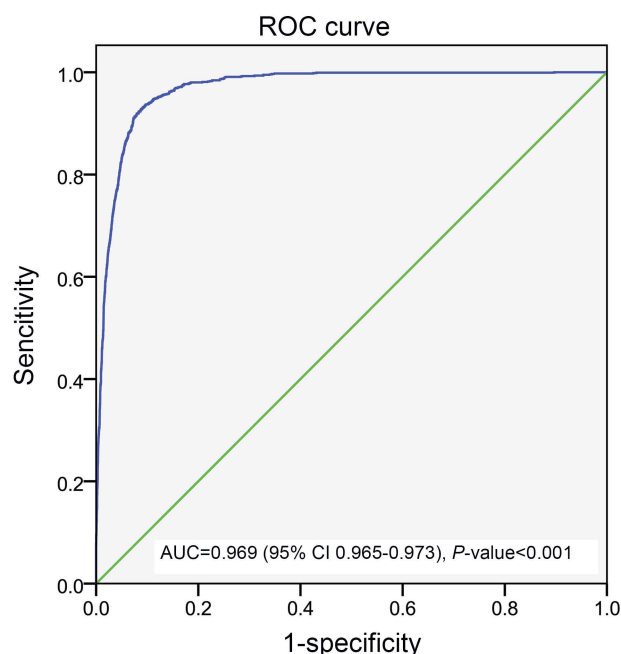
**Table 1** Baseline characteristics of the study population in subgroups stratified by severity of lung function impairment

| Group | No.  | Age (years, M [Q <sub>1</sub> , Q <sub>3</sub> ]) | Male (no.) | Female (no.) |
|-------|------|---|------------|--------------|
| A     | 2985 | 68 (63, 73)                                       | 1725       | 1260         |
| B     | 1129 | 70 (65, 74)                                       | 674        | 455          |
| C     | 1066 | 71 (66, 75)                                       | 654        | 412          |
| D     | 837  | 71 (66, 76)                                       | 544        | 293          |
| E     | 1183 | 72 (68, 76)                                       | 775        | 408          |
| F     | 545  | 71 (67, 74.8)                                     | 409        | 136          |

**Notes:** Δ = change; % pred, percentage of the predicted value; Group A: FEV<sub>1</sub> ≥ 80% pred; Group B: 70% pred ≤ FEV<sub>1</sub> < 80% pred; Group C: 60% pred ≤ FEV<sub>1</sub> < 70% pred; Group D: 50% pred ≤ FEV<sub>1</sub> < 60% pred; Group E: 35% pred ≤ FEV<sub>1</sub> < 50% pred; Group F: FEV<sub>1</sub> < 35% pred.

function-impaired groups and Groups A–D were classified as not severely lung function-impaired groups.

According to FVC criteria in evaluating positive bronchodilator response (a change post-bronchodilator test in FVC ≥ 12% of baseline and ≥ 200 mL), the cutoff value of FEV<sub>3</sub> in evaluating positive bronchodilator test has been counted. A ROC curve was used to determine the best corresponding cutoff for FEV<sub>3</sub> (Figure 1). The area under the ROC curve was 0.969 (95% CI: 0.965–0.973,  $P < 0.001$ ). Post-bronchodilator test a change in FEV<sub>3</sub> ≥ 10% of baseline and ≥ 165 mL had the best sensitivity (92.5%) and specificity (90.4%), and there

**Figure 1** Receiver operating characteristic (ROC) curve showing the performance of FEV<sub>3</sub> in evaluating bronchodilator test based on FVC evaluation criteria.

**Abbreviation:** AUC, area under the curve.

was an excellent agreement between the two diagnostic cutoffs ( $\kappa = 0.737$ ;  $P < 0.001$ ).

Post-bronchodilator FEV<sub>1</sub> increased by ≥ 12% of baseline in 21% (1627) of subjects, but the percentage was reduced to 14.6% (1131) according to the criteria that both FEV<sub>1</sub> changed ≥ 12% of baseline and ≥ 200 mL. Similar results were observed with FEV<sub>3</sub> and FVC (Table 2). Out of the 496 subjects with post-bronchodilator increase in FEV<sub>1</sub> by ≥ 12% of baseline but < 200 mL, 389 were in the severely lung function-impaired group (213 cases, 18% in Group E; 176 cases, 32.3% in Group F). There was a significant difference in the frequency of patients between the severely lung function-impaired group and the not severely lung function-impaired group ( $\chi^2 = 962.77$ ,  $P < 0.001$ ) (Table 3, Figure 2).

Significant bronchodilation is regarded as a change in post-bronchodilator FEV<sub>1</sub> or FVC ≥ 12% of baseline and ≥ 200 mL according to the ATS/ERS guidelines.<sup>4</sup> There were 314 subjects – mainly in the severely lung function-impaired groups (129 cases, 10.9% in Group E; 122 cases, 22.4% in Group F) – whose bronchodilator test was negative when evaluated with FEV<sub>1</sub>, but became positive with FVC. There was a significant difference in the frequency of patients between the severely lung function-impaired group and not-severely lung function-impaired group ( $\chi^2 = 626.97$ ,  $P < 0.001$ ) (Table 3, Figure 3). There were 593 subjects, mainly in the severely lung function-impaired groups, whose bronchodilator test was negative when evaluated with FEV<sub>1</sub> but was positive when evaluated with FEV<sub>3</sub> (196 cases, 16.6% in Group E; 136 cases, 25% in Group F). There was a significant difference in the frequency of patients between severely lung function-impaired group and not severely lung function impaired ( $\chi^2 = 420.14$ ,  $P < 0.001$ ). (Table 3, Figure 4).

The post-bronchodilator changes in the z score of FEV<sub>1</sub>, FVC and FEV<sub>3</sub> were related to the severity of lung function impairment (Table 4, Figure 5). As the severity increased, ΔzFEV<sub>1</sub> after the bronchodilator test increased gradually and peaked in Groups D and E, but decreased in Group F. In contrast, ΔzFVC continued to increase with the increase in the severity of ventilatory impairment, which peaked in Group F. Post-bronchodilator changes in zFVC were less than zFEV<sub>1</sub> in Groups A, B and C (Group A  $z = -3.16$ , Group B  $z = -2.86$ , Group C  $z = -2.86$ , all  $P < 0.05$ ) and similar to ΔzFEV<sub>1</sub> in Group D ( $z = -0.27$ ,  $P > 0.05$ ). But in Groups E and F, ΔzFVC significantly exceeded ΔzFEV<sub>1</sub> (Group E  $z = -4.15$ , Group F  $z = -6.96$ , all  $P < 0.001$ ). Changes in zFEV<sub>3</sub> exhibited similar trends. Post-bronchodilator ΔzFEV<sub>3</sub> was less than or equal to the change in zFEV<sub>1</sub> for subjects in Groups A to D (Group A  $z = -2.03$ ,  $P < 0.05$ , Group B  $z = -1.51$ , Group C  $z = -0.98$ , Group

Table 2 Characteristics of bronchodilator response in the study population

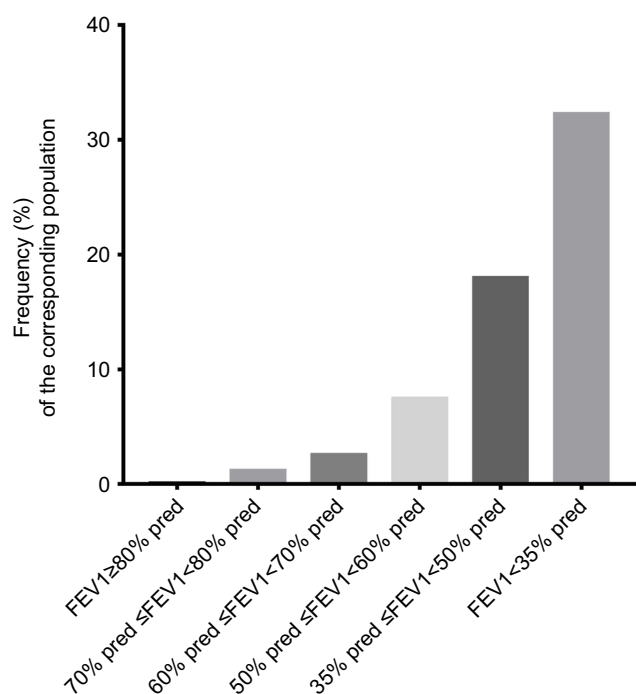
| Group  | No.<br>(%)      | Age (years, M<br>[Q <sub>1</sub> , Q <sub>3</sub> ]) | ΔFEV <sub>1</sub> % init≥12%<br>(%) | ΔFEV <sub>1</sub> %<br>init≥12% &<br>ΔFEV <sub>1</sub> ≥200 mL<br>(%) | ΔFEV <sub>3</sub> % init≥10%<br>(%) | ΔFEV <sub>3</sub> %<br>init≥10% &<br>ΔFEV <sub>3</sub> ≥165 mL<br>(%) | ΔFVC % init≥12%<br>(%) | ΔFVC %<br>init≥12% &<br>ΔFVC≥200 mL<br>(%) |
|--------|-----------------|--|-------------------------------------|---|-------------------------------------|---|------------------------|--|
| Male   | 4781<br>(61.7%) | 72<br>(67–77)  | 22.2                                | 16.6  | 24.1                                | 22.8  | 21.4                   | 17.4                                       |
| Female | 2964<br>(38.3%) | 70<br>(65–74)  | 19.1                                | 11.4  | 20.5                                | 16.8  | 18.3                   | 12.9                                       |
| Total  | 7745<br>(100%)  | 71<br>(66–76)  | 21                                  | 14.6  | 22.7                                | 20.5  | 20.2                   | 15.6                                       |

Notes: Δ= change; % init = percentage of the initial value.

Table 3 Characteristics of post-bronchodilator response in subgroups stratified by level of lung function impairment

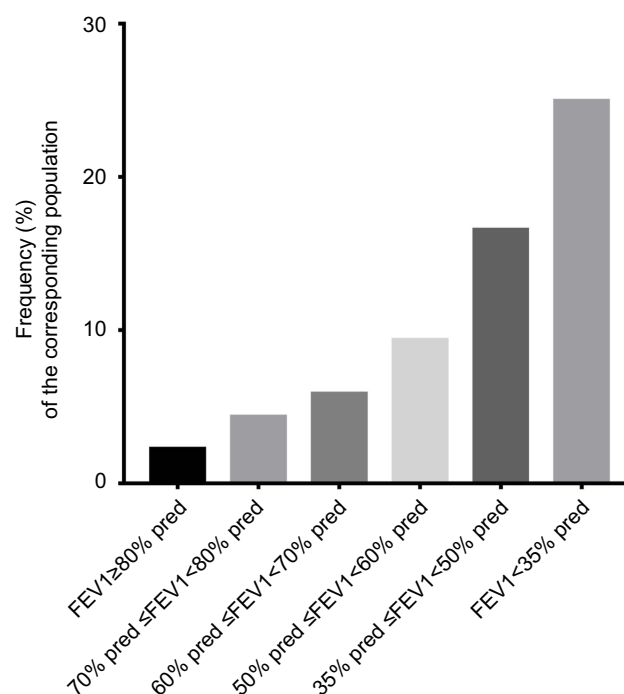
| Group | No.  | Age (years, M [Q <sub>1</sub> , Q <sub>3</sub> ]) | ΔFEV <sub>1</sub> % init≥12% &<br>ΔFEV <sub>1</sub> <200 mL (n) | Become positive with ΔFVC response (n) | Become positive with ΔFEV <sub>3</sub> response (n) |
|-------|------|---|---|--|---|
| A     | 2985 | 70 (65, 75)                                       | 2   | 2                                      | 69  |
| B     | 1129 | 71 (66, 77)                                       | 14  | 9                                      | 50  |
| C     | 1066 | 72 (67, 76)                                       | 28  | 18                                     | 63  |
| D     | 837  | 73 (66, 77)                                       | 63  | 34                                     | 79  |
| E     | 1183 | 73 (68, 77)                                       | 213   | 129                                    | 196   |
| F     | 545  | 71 (66, 76)                                       | 176   | 122                                    | 136   |

Notes: Δ= change; % init, percentage of the initial value; % pred, percentage of the predicted value; Group A: FEV<sub>1</sub>≥80% pred; Group B: 70% pred≤FEV<sub>1</sub><80% pred; Group C: 60% pred≤FEV<sub>1</sub><70% pred; Group D: 50% pred≤FEV<sub>1</sub><60% pred; Group E: 35% pred≤FEV<sub>1</sub><50% pred; Group F: FEV<sub>1</sub><35% pred.



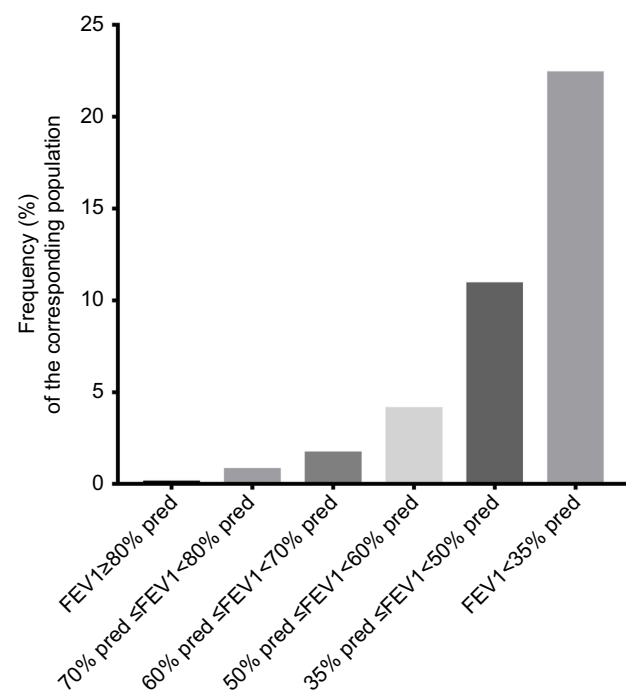
**Figure 2** Frequency distribution of subjects in each group showing post-bronchodilator change in FEV<sub>1</sub> of more than 12% of baseline but ≤200 mL in various subgroups stratified by level of lung function impairment.

**Note:** Δ = change.



**Figure 4** Frequency distribution of subjects in each group whose post-bronchodilator responses become positive with ΔFEV<sub>3</sub> response in various subgroups stratified by level of lung function impairment.

**Note:** Δ = change.



**Figure 3** Frequency distribution of subjects in each group whose post-bronchodilator responses become positive with ΔFVC response in various subgroups stratified by level of lung function impairment.

**Note:** Δ = change.

D  $z = -0.68$ ,  $P > 0.05$ ), but in Groups E and F,  $\Delta zFEV_3$  significantly exceeded  $\Delta zFEV_1$  (Group E  $z = -3.16$ ,  $P < 0.05$ , Group F  $z = -4.41$ ,  $P < 0.001$ ). Similar results were obtained after subgroup analysis of male and female subjects (Tables 4–6).

## Discussion

Elderly subjects – who are also the main population of COPD – are more prone to severe and fixed airways resistance. Increased airway resistance increases intrathoracic gas volume and results in diminished lung elastic recoil pressure.<sup>11</sup> After treatment with a bronchodilator, elderly patients – especially those with serious airflow limitation – report improvement in symptoms and exercise tolerance with little change in FEV<sub>1</sub>.<sup>12</sup> Although FEV<sub>1</sub> is a widely used efficacy end point, it cannot sensitively reflect the real change in lung function due to the improvement in airway obstruction.<sup>13</sup>

The bronchodilator test is a better guide to disease progression and can identify patients who might benefit from treatment with a bronchodilator.<sup>14</sup> In this study, we evaluated changes in lung function parameters before and after bronchodilator treatment to find appropriate indicators for evaluating lung function improvement in the elderly. The findings showed

Table 4 Spirometric Indexes expressed as change post-bronchodilator and z scores in subgroups stratified by level of lung function impairment

| Group | No.  | Age (years, M [Q <sub>1</sub> , Q <sub>3</sub> ]) | $\Delta$ FEV <sub>1</sub> (mL, M [Q <sub>1</sub> , Q <sub>3</sub> ]) | $\Delta$ FVC (mL, M [Q <sub>1</sub> , Q <sub>3</sub> ]) | $\Delta$ FEV <sub>3</sub> (mL, M [Q <sub>1</sub> , Q <sub>3</sub> ]) | $\Delta$ FEV <sub>1</sub> /M [Q <sub>1</sub> , Q <sub>3</sub> ]) | $\Delta$ FVC/M [Q <sub>1</sub> , Q <sub>3</sub> ]) | $\Delta$ zFEV <sub>3</sub> /M [Q <sub>1</sub> , Q <sub>3</sub> ]) |
|-------|------|---|--|---|--|--|--|---|
| A     | 2985 | 70 (65, 75)                                       | 40 (-30, 40)   | 30 (-75, 150)   | 30 (-50, 120)  | -0.28 (-0.74, 0.26)  | -0.33 (-0.76, 0.16)                                | -0.32 (-0.76, 0.17)   |
| B     | 1129 | 71 (66, 77)                                       | 70 (0, 150)  | 70 (-50, 190)   | 60 (-20, 160)  | -0.07 (-0.54, 0.46)  | -0.17 (-0.66, 0.32)                                | -0.16 (-0.59, 0.39)   |
| C     | 1066 | 72 (67, 76)                                       | 70 (0, 170)  | 80 (-30, 220)   | 80 (-10, 190)  | -0.07 (-0.54, 0.60)  | -0.13 (-0.58, 0.45)                                | -0.05 (-0.54, 0.55)   |
| D     | 837  | 73 (66, 77)                                       | 90 (10, 190)   | 140 (0, 295)  | 110 (10, 220)  | 0.06 (-0.48, 0.73)   | 0.12 (-0.46, 0.76)                                 | -0.11 (-0.43, 0.71)   |
| E     | 1183 | 73 (68, 77)                                       | 90 (20, 170)   | 160 (20, 330)   | 110 (20, 240)  | 0.06 (-0.41, 0.60)   | 0.20 (-0.37, 0.90)                                 | 0.11 (-0.37, 0.82)  |
| F     | 545  | 71 (66, 76)                                       | 80 (30, 160)   | 230 (60, 405)   | 130 (40, 250)  | 0 (-0.34, 0.52)  | 0.49 (-0.21, 1.21)                                 | 0.22 (-0.27, 0.88)  |

Notes:  $\Delta$ = change; % pred, percentage of the predicted value; Group A: FEV<sub>1</sub> ≥80% pred; Group B: 70% pred ≤ FEV<sub>1</sub> <80% pred; Group C: 60% pred ≤ FEV<sub>1</sub> <70% pred; Group D: 50% pred ≤ FEV<sub>1</sub> <60% pred; Group E: 35% pred ≤ FEV<sub>1</sub> <50% pred; Group F: FEV<sub>1</sub> <35% pred.

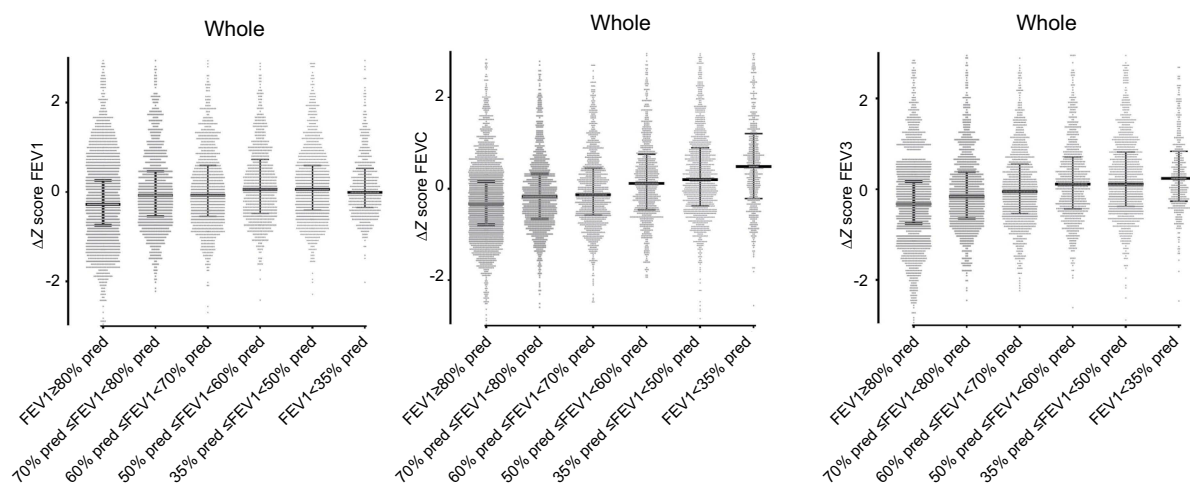
that there were notably more subjects in the severely lung function-impaired group exhibiting significant improvement in FEV<sub>3</sub> or FVC with less change in FEV<sub>1</sub> in response to the bronchodilator test (FEV<sub>1</sub> less than 50% predicted value). To minimize any bias due to age, height and weight, we also expressed values or changes as z scores. The z scores indicate the standard deviation of a measurement that differed from, the average predicted value, which was free of any bias. Hence, this result showed that an increase in airflow obstruction increased  $\Delta$ FEV<sub>1</sub> followed by a decline, while  $\Delta$ FVC and  $\Delta$ FEV<sub>3</sub> increased progressively. In subjects with mild respiratory defect,  $\Delta$ FEV<sub>3</sub> or  $\Delta$ FVC was less than or equal to  $\Delta$ FEV<sub>1</sub>, but  $\Delta$ FEV<sub>3</sub> or  $\Delta$ FVC exceeded the relative change in FEV<sub>1</sub> in severely lung function-impaired group. Results also indicated that FEV<sub>3</sub> and FVC are sensitive indicators of bronchodilation in severe airway obstruction, whereas FEV<sub>1</sub> is more sensitive in assessing bronchodilation in mild ventilatory dysfunction.

It has been reported that acute FVC response to bronchodilators was significantly more correlated with health-related quality of life than FEV<sub>1</sub> response.<sup>15</sup> Using the criterion of “clinically significant” to describe an increase in FVC, FEV<sub>1</sub> (≥12% of pre-bronchodilator and ≥0.2 L) or FEV<sub>3</sub> (≥10% of pre-bronchodilator and ≥0.165 L), we observed that FVC and FEV<sub>3</sub> were better measurements for assessing reversibility than FEV<sub>1</sub>, especially in patients with severely impaired lung function. Also, there was a strong correlation between FEV<sub>3</sub> and FVC in assessing the responsiveness to bronchodilator. Repeated FVC can be stressful in aged patients with severe obstruction.<sup>5</sup> Thus, it seems that when FVC is not reliable, FEV<sub>3</sub> might have special clinical application value in detecting bronchial reversibility.

Our study presents new data on FEV<sub>3</sub> implying its clinical applicability for better interpretation of reversibility monitoring, particularly in severely impaired patients who cannot blow for ≥6 s even after their best attempts. Larger FEV<sub>3</sub> and FVC responses can provide useful information regarding reduction of hyperinflation with beneficial effects on dyspnea, exercise tolerance and function of small airways,<sup>16</sup> which has important clinical application value.

FEV<sub>6</sub> has been proposed as an alternative to FVC. Our previous research<sup>17</sup> found that FEV<sub>6</sub> strongly correlated with FVC which did not vary with the forced expiratory time and it could be used as a valid alternative to FVC in diagnosing airflow obstruction in elderly males. FEV<sub>6</sub> is closer to FVC in terms of expiratory time, whereas FEV<sub>3</sub> is between FEV<sub>1</sub> and FEV<sub>6</sub> in expiratory time. FEV<sub>3</sub> also makes spirometry easier, faster and safer than FVC measurement and does not correlate with forced expiratory time.





**Figure 5** Post-bronchodilator change in z score of FEV<sub>1</sub> (left) is larger in 70% pred≤FEV<sub>1</sub><80% pred group, 60% pred≤FEV<sub>1</sub><70% pred group and 50% pred≤FEV<sub>1</sub><60% pred group compared with FEV<sub>1</sub>≥80% pred group and declines as obstruction becomes most severe. Conversely, the post-bronchodilator effect on FVC (middle) increased with the severity of lung function impairment. The patterns for FEV<sub>3</sub> and FVC are similar. Thin lines, 5th and 95th percentiles; central thick line, median.

**Note:** Δ= change; % pred, percentage of the predicted value.

**Table 5** Spirometric Indexes in male subjects expressed as change in post-bronchodilator and z scores in subgroups stratified by level of lung function impairment

| Group | No.  | Age (years, M [Q <sub>1</sub> , Q <sub>3</sub> ]) | ΔFEV <sub>1</sub> (mL, M [Q <sub>1</sub> , Q <sub>3</sub> ]) | ΔFVC (mL, M [Q <sub>1</sub> , Q <sub>3</sub> ]) | ΔFEV <sub>3</sub> (mL, M [Q <sub>1</sub> , Q <sub>3</sub> ]) | ΔzFEV <sub>1</sub> (M [Q <sub>1</sub> , Q <sub>3</sub> ]) | ΔFVC (M [Q <sub>1</sub> , Q <sub>3</sub> ]) | ΔzFEV <sub>3</sub> (M [Q <sub>1</sub> , Q <sub>3</sub> ]) |
|-------|------|---|--|---|--|---|---|---|
| A     | 1725 | 71 (66, 77)                                       | 40 (−30, 130)  | 30 (−80, 160)                                   | 30 (−60, 130)  | −0.31 (−0.81, 0.25)                                       | −0.38 (−0.79, 0.11)                         | −0.36 (−0.81, 0.14)                                       |
| B     | 674  | 72 (66, 77)                                       | 70 (0, 160)  | 70 (−50, 220)                                   | 70 (−22.5, 190)  | −0.12 (−0.56, 0.44)                                       | −0.23 (−0.68, 0.33)                         | −0.16 (−0.62, 0.44)                                       |
| C     | 654  | 73 (67, 78)                                       | 90 (0, 200)  | 90 (−30, 260)                                   | 90 (−10, 220)  | 0 (−0.56, 0.69)   | −0.16 (−0.61, 0.48)                         | −0.62 (−0.56, 0.59)                                       |
| D     | 544  | 73 (68, 78)                                       | 100 (20, 220)  | 170 (10, 330)                                   | 130 (12.5, 250)  | 0.06 (−0.44, 0.81)  | 0.14 (−0.46, 0.74)                          | 0.14 (−0.45, 0.74)  |
| E     | 775  | 73 (67, 78)                                       | 100 (20, 200)  | 190 (30, 380)                                   | 130 (30, 280)  | 0.06 (−0.44, 0.81)  | 0.21 (−0.38, 0.93)                          | 0.14 (−0.36, 0.89)  |
| F     | 409  | 72 (66, 76)                                       | 90 (30, 180)   | 250 (60, 430)                                   | 150 (50, 270)  | 0 (−0.37, 0.56)   | 0.44 (−0.27, 1.12)                          | 0.24 (−0.26, 0.84)  |

**Notes:** Δ= change; % pred, percentage of the predicted value; Group A: FEV<sub>1</sub>≥80% pred; Group B: 70% pred≤FEV<sub>1</sub><80% pred; Group C: 60% pred≤FEV<sub>1</sub><70% pred; Group D: 50% pred≤FEV<sub>1</sub><60% pred; Group E: 35% pred≤FEV<sub>1</sub><50% pred; Group F: FEV<sub>1</sub><35% pred.

In addition, FEV<sub>3</sub> has unique application advantages in patients who cannot exhale for 6 s. In such subjects, addition of FEV<sub>3</sub> in the daily practice of pulmonary medicine will help physicians to find clinically important relief for hyperinflation.

One of the strengths of our study is that we discussed unselected data on bronchodilator response across various lung function impairment in an aging population. Also, the subjects involved in this study were not limited to any disease or a diagnosis of airflow obstruction. The result reflected the characteristics of common clinical practices in the real world, thus highlighting their clinical usefulness. However, the present study also has some limitations. Being a retrospective study, it failed to provide information about clinical symptoms and disease severity of the subjects. It also lacked information about the use of medication before spirometry. The lung

function tests were part of the routine clinical maneuvers, and some subjects might not have withheld medications before testing which may have led to an underestimation of bronchodilator responsiveness. Another significant caveat is the lack of specific diagnosis-related subgroup analyses, which requires further study in the future.

Currently, FEV<sub>3</sub> can be recorded with many spirometers. Thus, according to the result of our study, we encourage to report and analyze FEV<sub>3</sub> for better assessment of spirometry. Compared with the score of the clinical symptom and life quality, parameters of spirometry such as FEV<sub>3</sub> are more objective. Sensitive assessment of improvement in pulmonary function is helpful for disease evaluation and treatment options. However, correlations between the characteristic changes in FEV<sub>3</sub> and subsequent clinical manifestations remains to be further studied.

Table 6 Spirometric Indexes in female subjects expressed as change in post-bronchodilator and z-scores in subgroups stratified by level of lung function impairment

| Group | No.  | Age (years, M [Q <sub>1</sub> , Q <sub>3</sub> ]) | ΔFEV <sub>1</sub> (mL, M [Q <sub>1</sub> , Q <sub>3</sub> ]) | ΔFVC (mL, M [Q <sub>1</sub> , Q <sub>3</sub> ]) | ΔFEV <sub>3</sub> (mL, M [Q <sub>1</sub> , Q <sub>3</sub> ]) | ΔzFEV <sub>1</sub> [M (Q <sub>1</sub> , Q <sub>3</sub> )] | ΔzFVC (M [Q <sub>1</sub> , Q <sub>3</sub> ]) | ΔzFEV <sub>3</sub> (M [Q <sub>1</sub> , Q <sub>3</sub> ]) |
|-------|------|---|--|---|--|---|--|---|
| A     | 1260 | 68 (63, 73)                                       | 40 (-30, 100)  | 20 (-70, 120)                                   | 30 (-40, 110)  | -0.21 (-0.75, 0.26)                                       | -0.29 (-0.76, 0.22)                          | -0.25 (-0.71, 0.28)                                       |
| B     | 455  | 70 (65, 74)                                       | 60 (0, 130)  | 60 (-40, 170)                                   | 30 (-40, 110)  | -0.05 (-0.52, 0.49)                                       | -0.09 (-0.60, 0.48)                          | -0.12 (-0.58, 0.41)                                       |
| C     | 412  | 71 (66, 75)                                       | 70 (0, 140)  | 60 (-40, 170)                                   | 50 (-20, 130)  | 0.02 (-0.52, 0.57)  | -0.09 (-0.60, 0.48)                          | -0.08 (-0.58, 0.61)                                       |
| D     | 293  | 71 (66, 76)                                       | 70 (10, 155)   | 100 (-10, 215)                                  | 55 (-20, 160)  | 0.02 (-0.44, 0.69)  | 0.12 (-0.45, 0.71)                           | -0.15 (-0.42, 0.75)                                       |
| E     | 408  | 72 (68, 76)                                       | 60 (10, 130)   | 110 (10, 240)                                   | 90 (5, 180)  | -0.05 (-0.44, 0.49)                                       | 0.17 (-0.35, 0.84)                           | 0.12 (-0.38, 0.75)  |
| F     | 136  | 71 (67, 74.8)                                     | 70 (20, 130)   | 190 (50, 310)                                   | 85 (10, 180)   | 0.02 (-0.36, 0.49)  | 0.58 (-0.35, 0.84)                           | 0.18 (-0.32, 0.95)  |

Notes: Δ= change; % pred, percentage of the predicted value; Group A: FEV<sub>1</sub> ≥80% pred; Group B: 70% pred ≤ FEV<sub>1</sub> <80% pred; Group C: 60% pred ≤ FEV<sub>1</sub> <70% pred; Group D: 50% pred ≤ FEV<sub>1</sub> <60% pred; Group E: 35% pred ≤ FEV<sub>1</sub> <50% pred; Group F: FEV<sub>1</sub> <35% pred.

In summary, this population-based retrospective study showed that in elderly subjects, especially those with severe lung function impairment, FEV<sub>3</sub> combined with FVC can be a clinically effective and sensitive outcome measure to detect bronchial reversibility. In those elderly subjects who cannot complete ≥6 s of forced expiration and whose FVC is not reliable, FEV<sub>3</sub> combined with FEV<sub>1</sub> can be clinically valuable in detecting bronchial reversibility.

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## Disclosure

The authors report no conflict of interest in this work.

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